Integrating depression and acute coronary syndrome care in low resource hospitals in China: the I-CARE randomised clinical trial

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Summary

Background Acute coronary syndrome (ACS) often co-occurs with depression, which adversely affects prognosis and increases medical costs, but effective treatment models are lacking, particularly in low-resource settings. This study aims to determine the effectiveness of an ACS and depression integrative care (IC) model compared to usual care (UC) in improving depression symptoms and other health outcomes among patients discharged for ACS in Chinese rural hospitals.

Methods A multicentre, randomised controlled trial was conducted in sixteen rural county hospitals in China, from October 2014 to March 2017, to recruit consecutively all ACS patients aged 21 years and older after the disease stablised and before discharge. Patients were randomly assigned in a 1:1 ratio to receive either the IC or UC, stratified by hospital and depression severity. Patients allocated to IC received an ACS secondary prevention program and depression care including case screening, group counselling, and individual problem-solving therapy. Patients allocated to UC received usual care. The primary outcome was change in Patient Health Questionnaire-9 (PHQ-9) from baseline to 6 and 12 months. Main secondary outcomes included major adverse events (MAEs) composed of all-cause death, non-fatal myocardial infarction and stroke, and all-cause re-hospitalisation. Participants were followed up till March 2018. All data were collected in person by trained assessors blinded to treatment group and MAEs were adjudicated centrally. This trial is registered with ClinicalTrials.gov, NCT02195193.

Findings Among 4041 eligible patients (IC: 2051; UC: 1990), the mean age was 61 ± 10 years and 63% were men. The mean PHQ-9 score lowered at both 6 and 12 months in both groups but was not lower in IC compared to UC at 6 months (mean difference (MD): −0.04, 95% confidence interval (CI): −0.20, 0.11) or 12 months (MD: −0.06, 95% CI: −0.21, 0.09). There were no treatment group differences for MAEs or other secondary outcomes except for secondary prevention medications at 12 months (45.2% in IC vs 40.8% in UC; relative risk: 1.21, 95% CI: 1.05–1.40). Pre-specified subgroup analyses showed that IC, compared to UC, may be more effective in lowering PHQ-9 scores in women, older patients, and patients with low social support, but less effective in moderately and severely depressed patients (all p for interaction <0.05).

Interpretation The study found that the cardiology nurse-led ACS- and depression-integrated care, compared to usual care, did not improve depression symptoms in all patients discharged with ACS. Greater benefits in certain subgroups warrants further studies.

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Research in context

Evidence before this study

We searched PubMed and Cochrane databases from inception until Nov 1, 2023, using the search terms "integrated", "collaborative care", "depression", "cardiovascular", and "acute coronary syndrome", with no language restrictions. Prior trials of depression treatment in patients with both depression and ACS, conducted mainly in the United States and Europe, generally have showed that collaborative care models modestly improve depressive symptoms but with little effect on clinical outcomes. However, the generalisability was limited to patients with comorbid depression and ACS, and graded intervention based on depression severity was not considered in these studies. It is not yet clear whether existing strategies will work for patients in other health systems.

Added value of this study

Low- and middle-income countries have limited specialised psychiatric services. Whether training cardiology nurses to treat depression for patients with ACS is effective has great public health importance but remains unanswered. To our knowledge, this is the largest randomised controlled trial testing the effect of an ACS and depression integrated care intervention in reducing depression symptoms and improving cardiovascular outcomes in unselected patients with ACS and, to our knowledge, is also the first such study conducted in resource-limited clinical settings. We reported that a cardiology nurse-coordinated depression care integrated into ACS care (IC) was not more effective than usual care (UC) in rural county hospitals. However, the pre-specified subgroup analysis showed that sex, social support and severity of depression may affect the efficacy of the intervention, with some benefit for select patients.

Implications of all the available evidence

The collaborative care model may reduce depression symptoms for depressed ACS patients in high resource settings. However, compared with usual care, the benefits of integrating depression care into ACS secondary care remains unclear in both high and low resource settings. Future research in low-resource settings is needed to determine if enhanced psychiatric training for nursing personnel would improve treatment outcomes or if greater attention to patient selection is needed to benefit from collaborative care intervention.

Introduction

Depression and acute coronary syndrome (ACS) are common conditions and represent important public health challenges worldwide.[1,2] As the most common mental illness in China,[3] depression often coexists with ACS,[4,5] which adversely affects prognosis[6,7] and increase costs.[8] Based upon available epidemiologic evidence, the American Heart Association has recognised depression as a risk factor for poor prognosis in patients with ACS.[9]

Prior trials of depression treatment in patients with both depression and ACS have showed small or no benefit.[10,11] Collaborative care models in depressed ACS patients have been shown to modestly improve depressive symptoms but with little effect on clinical outcomes.[12–14] These studies were mainly conducted in the United States and Europe, the generalisability was limited only to patients with comorbid depression and ACS. Whether the existing strategies are suitable for patients from Asia and other health systems remains unknown.

Treatments for mental illness and cardiovascular disease are separate under the existing Chinese healthcare system. China's resources for mental health care are generally extremely limited, particularly in rural areas.[15,16] Lack of resources and awareness represent substantial barriers to quality care for patients with comorbid mental health disorders and other chronic illnesses. Therefore, an innovative model that integrates depression care into major chronic disease care and allows mental health care task-shifting from specialist services to non-specialist services is urgently needed in low-resource areas. Task shifting has been conducted in other countries and the feasibility of this concept has been established.[17,18]

The Integrating Depression Care in Management of ACS Patients in Low Resource Hospitals in China (I-CARE) study was initiated to determine the effectiveness of an ACS and depression integrative care (IC) model compared to usual care (UC) in reducing depression symptoms, improving cardiovascular outcomes and quality of life, and reducing medical expenses among patients discharged for ACS.[19]

Methods

Study design

I-Care is a randomised clinical trial conducted in low-resource county hospitals in China. The study protocol

has been published elsewhere.[19] Briefly, eligible patients from these hospitals were recruited from October 2014 through March 2017 and randomised to either IC or UC for the corresponding treatments. All study patients would be followed up at 6- and 12-month for depression symptoms with PHQ-9 and until the end of the study on March 24, 2018 for major adverse events. The Peking University Institutional Review Board reviewed and approved the study, and all study patients provided written informed consent. An independent data and safety monitoring committee oversaw the trial and reviewed the trial data for patient safety at regular intervals. The study was registered on the ClinicalTrials.gov (NCT02195193).

Participants

Men and women, aged 21–79 years, and hospitalised for a definite diagnosis of ACS including ST-elevation myocardial infarction (STEMI), non–ST-elevation myocardial infarction (NSTEMI) or unstable angina (UA) were recruited after the disease stabilised and before discharge. The main exclusion criteria were diagnosis of bipolar disorder, schizophrenia, psychotic depression, or acute suicidality, alcohol dependent, severe medical comorbidity that indicated a life expectancy less than 12 months, and inability to communicate or to provide written informed consent.

Assessments

Data were collected at baseline and at 6- and 12-month in person by trained assessors blinded to treatment group, including 1) social demographic information and lifestyle habits with an interview questionnaire[20,21]; 2) diagnosis of ACS, prior history of CVD, prior and current medical treatments via chart review; 3) depression symptoms assessed by the 9-item Patient Health Questionnaire (PHQ-9)[22]; 4) quality of life by EuroQol 5 dimensions for health status (EQ5D)[23]; 5) and social support by the 5-item ENRICHD Social Support Inventory (ESSI-5).[24] The generalised anxiety disorders scale-7 (GAD-7)[25,26] was added to the assessment battery as a measure of anxiety in May 2016. In addition, the Beck Depression Inventory-II (BDI-II) and Perceived Social Support Scale (PSSS) scores were obtained from study participants in 4 of the 16 study hospitals.

Major adverse events (MAEs), defined as a composite outcome including all-cause death, non-fatal myocardial infarction and stroke, and re-hospitalisation for any reason, were collected at 6- and 12-month and annually until March 24, 2018, through chart review and telephone interview and were adjudicated by a centrally-based medical officer who was blind to treatment groups.

Randomisation and masking

After the baseline evaluation, patients were randomly assigned in a 1:1 ratio to receive either the IC or UC. To ensure concealment of the treatment allocation, randomisation was performed centrally using a web-based IT system. The randomisation was stratified by hospitals and the severity of depression measured by the 9-item Patient Health Questionnaire (PHQ-9)[22] (PHQ-9 score <10 or ≥10). Permuted blocks were used with a randomly ordered size of 4, 6 and 8. The IT system informed the interventionist automatically which patient had been allocated to the IC group, and then the interventionist, a trained cardiology nurse, would initiate the intervention before the patient was discharged. The outcomes assessor had no knowledge of the group allocation of any patient.

Treatments

The usual care (UC) was the standard ACS care model adopted in the CPACS-3 study[27] that was limited to inpatient ACS care plus usual clinic follow up visits. In addition to the usual care, patients in the IC group received a nurse-coordinated multifaceted treatment that integrated an ACS secondary prevention program after discharge and a depression care package that was initiated at discharge.

The ACS secondary prevention program included the prescription of evidence-based ACS secondary prevention medications at discharge and reinforcing medication adherence, advising healthy lifestyle changes, checking blood pressure measurements at months 1, 2, 3, 5 and 11 after discharge for all participants.

The depression care included: 1) Screening for depression and anxiety at discharge and within 3 months after discharge. 2) Specific treatment of depression and anxiety guided by the PHQ-9 and GAD-7 scores. Patients with a PHQ-9 ≥ 5 or GAD-7 ≥ 5 at any screening were invited to group counselling, while patients with a PHQ-9 ≥ 10 or GAD-7 ≥ 10 were offered additional individual counselling. Group counselling was composed of four sessions, once a month, provided by trained nurses. Individual counselling was provided biweekly using problem-solving therapy[28] for at least four sessions by the same nurses.

Further details on the treatments appeared in the published protocol.[19]

Study outcomes

The primary outcome was the trend of change in mean PHQ-9 score during the one year of intervention. Secondary outcomes included the following: 1) Incidence of MAEs after discharge; 2) Proportion of patients with PHQ-9 score or GAD-7 score less than 5; 3) Proportion of patients with the use of evidence-based ACS secondary prevention medication, defined as self-reported currently taking any 4 or more of aspirin, clopidogrel, statins, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), and β-blockers; 4) Change in EQ5D score from baseline to 6 and 12 months; 5) Proportion of patients with controlled blood pressure

(systolic blood pressure ≤140 mmHg and diastolic blood pressure ≤90 mmHg); 6) proportion of patients with self-reported healthy lifestyle (a composite measure including physical activity ≥3 times/week and more than 30 min each time, no smoking, no alcohol use, and body mass index <24 kg/m^2); 7) Change in GAD-7 scores from baseline to 6 and 12 months; 8) Change in BDI-II and PSSS scores from baseline to 6 months and 12 months (measured in a subsample of patients).

Statistical analysis

For the primary outcome, we estimated that 4000 participants would provide at least 90% power to detect an effect size of 0.7 in mean change of PHQ-9 score from the baseline, with a 5% significance level and a pooled standard deviation of 6, assuming that the loss to follow-up is 20%.

The primary analysis was performed according to the intention to treat principle. Missing data was handled by the maximum likelihood estimation of the mixed model, which is known as an effective method for dealing with missing data on repeated measures.[29] The PHQ-9 score was the repeated independent variable, allowing all 4041 participants with baseline PHQ-9 score to be included. Hospital-level and subject-level random-effect intercepts and hospital-level random slope were incorporated for considering the clustering effect. The unstructured covariance structure was used in modeling the random effects.[29] The treatment effect was represented by an interaction between time of measurement (i.e. baseline, 6 months and 12 months) and treatment group.[19] Mean differences between treatment groups and its 95% confidence intervals (CIs) at each follow-up time point are reported. Sensitivity analysis was done with adjustment for potential confounding factors including age, sex, type of ACS, severity of depression and level of social support.

We performed subgroup analyses on the effect on primary outcome, stratified by pre-specified variables: age (<65, ≥65), sex (M/F), subtype of ACS (MI, UA), severity of depression and anxiety (PHQ-9 and/or GAD-7 scores, <5, 5–9, ≥10), and level of social support (high, low). Low social support defined as ESSI score ≤3 on 2 or more items and a total score <18.[30] The subgroup analyses were conducted with the change in PHQ-9 score from baseline as the dependent variable and the interaction term of treatment group and the subgroup variable as the independent variable. This was performed respectively for the change to 6-month and the change to 12-month and separately for each pre-specified variable, among participants with both the baseline and follow up PHQ-9 data available.

Generalised linear mixed models were used to estimate treatment effects for binary secondary outcomes and linear mixed models were used for continuous secondary outcomes. Hospital was treated as a fixed covariate, and log-binomial distributions were replaced with logistic distributions for binary secondary outcomes. For the MAEs, the time to event was defined as the time from randomisation to the time the event occurred or the end of the trial, whichever came first. Log-rank tests were used to detect the difference of event rate between treatment groups. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs.

We did not adjust for multiple tests and hence all results on secondary outcomes as well as those from the subgroup analysis should be considered exploratory.

All statistical tests were performed at a significance level of 0.05 of two sides. All analyses were performed using SAS version 9.4 (SAS Institute Inc).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study participants

Out of the initial 20 hospitals contacted, 2 declined participation, and 2 withdrew, due to their inability to meet the study requirements on data quality. The remaining 16 hospitals enrolled a total of 4041 patients with ACS, who were randomised to the IC group (n = 2051) or UC group (n = 1990; Fig. 1) from October 2014 to March 2017. Patients were predominantly male (63%) and mean age was 61 years. The mean baseline PHQ-9 score was 3.6 and 3.3% patients had a PHQ-9 score ≥10. Baseline characteristics were similar between treatment groups (Table 1).

Adherence to treatment

Among all patients allocated to IC, 80.7% received the ACS secondary prevention program for at least five sessions. Among 759 patients who met the criteria for group counselling, 68.3% completed the four required sessions. Among 83 patients who met the criteria for individual counselling, 89.2% completed at least the required four sessions (Table 2). Five patients in IC and three patients in UC had suicide attempts during the study duration (p = 0.516). These patients were referred to psychiatrist and family members informed as per the protocol.

Primary outcome

In the UC group, mean PHQ-9 scores fell from 3.64 (3.02) at baseline to 2.19 (2.23) at 6 months (p < 0.001) and 2.00 (2.23) at 12 months (p < 0.001); for those randomised to IC, mean PHQ-9 scores fell from 3.62 (3.01) at baseline to 2.14 (2.19) at 6 months (p < 0.001)

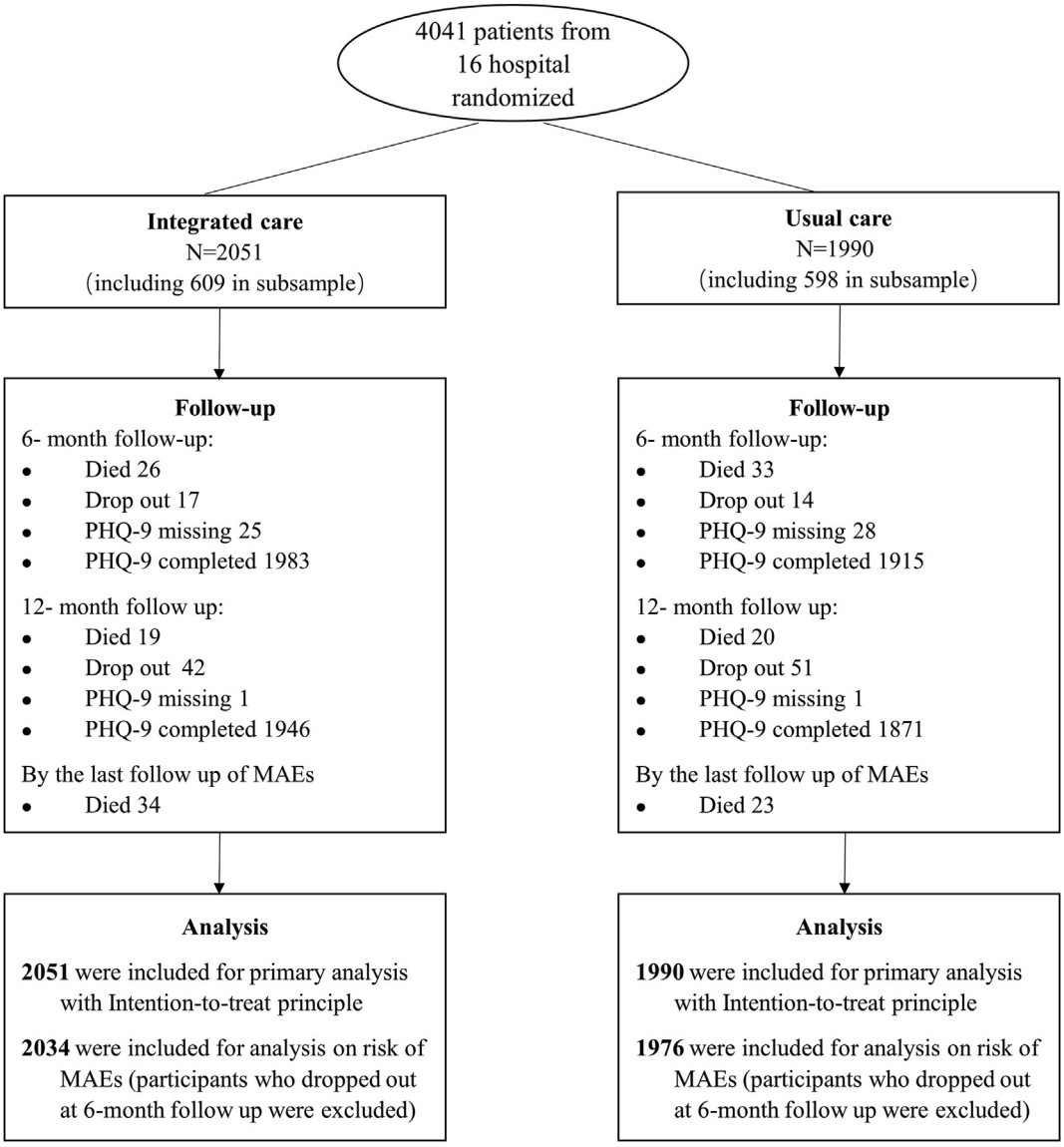

Fig. 1: CONSORT chart displaying participant enrollment.

and 1.94 (2.18) at 12 months ($p < 0.001$). However, the PHQ-9 scores were not different between groups at either 6- (mean difference, –0.04; 95% CI, –0.20 to 0.11) or 12- months (mean difference, –0.06; 95% CI, –0.21 to 0.09) (time by treatment group interaction, $p = 0.436$) (Fig. 2). The sensitivity analysis with adjustment for covariates did not change this finding (P for interaction = 0.377).

Pre-specified subgroup analysis showed that the treatment effect with IC compared to UC on PHQ-9 score at 12 months tend to be greater in women compared to men (–0.26 vs 0.02, p for interaction<0.001), in older compared to younger patients (–0.18 vs –0.01, $p = 0.026$), and in patients with low compared to high social support at baseline (–0.35 vs –0.04, $p < 0.001$). However, reductions in PHQ-9 scores were less in IC compared to UC among patients with more severe depression or greater anxiety symptoms at baseline (either PHQ-9 or GAD-7 ≥ 10, all $p < 0.001$). In contrast, reduction in PHQ-9 scores were more in IC compared to UC among patients with minimal depression. The subgroup analysis on the treatment effect at 6 months showed a similar pattern of results (Fig. 3).

Secondary outcomes

Results for effects on secondary outcomes are summarised in Table 3. During a median follow-up of 19.3 months, the MAEs rate was 28.5% for IC group and

Characteristic	Total (N = 4041)	Integrated care group (N = 2051)	Usual care group (N = 1990)
Age, mean (SD), y	61.1 (9.6)	61.2 (9.4)	61.0 (9.8)
Male, No. (%)	2555 (63.2)	1328 (64.8)	1227 (61.7)
Education, No. (%)			
None	733 (18.1)	340 (16.6)	393 (19.8)
Primary	1106 (27.4)	593 (28.9)	513 (25.8)
Secondary	1275 (31.6)	653 (31.8)	622 (31.3)
High school and above	927 (22.9)	465 (22.7)	462 (23.2)
Health insurance, No. (%)	3951 (97.8)	2009 (98.0)	1942 (97.6)
Diagnosis, No. (%)			
STEMI	1127 (27.9)	560 (27.3)	567 (28.5)
NSTEMI	605 (15.0)	305 (14.9)	300 (15.1)
UA	2309 (57.1)	1186 (57.8)	1123 (56.4)
History of disease, No. (%)[b]			
Myocardial Infarction	418 (10.3)	218 (10.6)	200 (10.1)
Angina pectoris	959 (23.7)	474 (23.1)	485 (24.4)
Heart failure	105 (2.6)	56 (2.7)	49 (2.5)
Stroke/TIA	358 (8.9)	185 (9.0)	173 (8.7)
Hypertension	2230 (55.2)	1171 (57.1)	1059 (53.2)
Diabetes	745 (18.4)	397 (19.4)	348 (17.5)
Dyslipidemia	193 (4.8)	93 (4.5)	100 (5.0)
Depression	42 (1.0)	22 (1.1)	20 (1.0)
Secondary prevention medications, No. (%)			
Aspirin	3817 (94.5)	1938 (94.5)	1879 (94.4)
clopidogrel	3022 (74.8)	1520 (74.1)	1502 (75.5)
statins	3802 (94.1)	1923 (93.8)	1879 (94.4)
ACEI/ARB	2120 (52.5)	1091 (53.2)	1029 (51.7)
β-blockers	2709 (67.0)	1367 (66.7)	1342 (67.4)
Any four of above	2762 (68.4)	1416 (69.0)	1346 (67.6)
Body Mass Index, mean (SD)[a]	24.6 (3.3)	24.6 (3.3)	24.6 (3.4)
Heart rate, mean (SD), beats/min	70 (9)	70 (9)	70 (9)
Systolic blood pressure, mean (SD), mmHg	123 (15)	123 (15)	123 (15)
Diastolic blood pressure, mean (SD), mmHg	73 (9)	74 (9)	73 (9)
Blood pressure <140/90 mmHg, No. (%)	3358 (83.1)	1691 (82.5)	1667 (83.8)
History of smoking, No. (%)	1137 (28.1)	597 (29.1)	540 (27.1)
High social support, No. (%)	3393 (84.0)	1734 (84.5)	1659 (83.4)
PHQ-9 score, mean (SD)	3.6 (3.0)	3.6 (3.0)	3.6 (3.0)
Severity of depression symptoms, No. (%)			
PHQ-9 score <5	2819 (69.8)	1432 (69.8)	1387 (69.7)
5 ≤PHQ-9 score <10	1088 (26.9)	550 (26.8)	538 (27.0)
PHQ-9 score ≥10	134 (3.3)	69 (3.4)	65 (3.3)
GAD-7 score, mean (SD)[b]	3.2 (3.0)	3.3 (3.0)	3.2 (3.0)
Severity of depression symptoms, No. (%)			
GAD-7 score <5	1354 (71.3)	684 (70.5)	670 (72.0)
5 ≤GAD-7 score <10	473 (24.9)	248 (25.6)	225 (24.2)
GAD-7 score ≥10	73 (3.8)	38 (3.9)	35 (3.8)
EQ5D, median [IQR]	0.8 [0.7, 1.0]	0.8 [0.7, 1.0]	0.8 [0.7, 1.0]
BDI-II score, median [IQR][c]	4 [2,8]	4 [2,7]	4 [2,9]
PSSS score, median [IQR][c]	70 [58, 78]	70 [59, 77]	70 [58, 78]

Abbreviation: STEMI, ST-Elevation Myocardial Infarction; NSTEMI, Non-ST-Elevation Myocardial Infarction; UA, Unstable Angina; MI, Myocardial Infarction; TIA, Transient ischemic attack; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalised Anxiety Disorder-7; EQ5D, EuroQol-5D; BDI-II, Beck Depression Inventory-II; PSSS, Perceived social support scale. [a]Calculated as weight in kilograms divided by height in meters squared. [b]Only measured in patients (n = 1900) who were recruited after May 2016. [c]Only measured in a subsample of patients from four hospitals (n = 1207).

Table 1: **Baseline patient demographic and clinical characteristics.**

Components of IC treatment	Frequency of treatment (times)	No. (%) of participants
ACS secondary prevention program attendance (n = 2051)	0	35 (1.7)
	1–4	360 (17.6)
	≥5	1656 (80.7)
Group counselling attendance (n = 759)	0	137 (18.1)
	1–3	104 (13.7)
	≥4	518 (68.3)
Individual counselling attendance (n = 83)	0	6 (7.2)
	1–3	3 (3.6)
	≥4	74 (89.2)

Abbreviation: IC, Integrated care.

Table 2: **Fidelity of different treatment components in IC group.**

27.0% for UC group. There was no significant difference for MAEs (HR: 1.06; 95% CI: 0.95, 1.20). The rate of MAEs excluding re-hospitalisations for any reason was 6.4% with IC and 6.1% with UC (HR: 1.12; 95% CI: 0.88, 1.42).

There also were no significant between-group differences in other secondary outcomes except for the secondary prevention medication use, which was significantly higher in the IC group at 12-month compared to the UC group (45.2% vs 40.8%, OR: 1.21, 95% CI: 1.05–1.40). To explore if the possible effect on secondary prevention medications was linked to depression care, we repeated the subgroup analysis as that done for the primary outcome and found a pattern matching to that on the effect on PHQ-9 scores by severity of depression, i.e favourable to the IC among patients with minimal depression but unfavourable to the IC among patients with mild or more severe depression, though the interaction term was not statistically significant (Figure S1).

Discussion

In this multicentre randomised clinical trial among Chinese patients with ACS, we found that the cardiology nurse-coordinated ACS and depression integrated care, compared with usual care, did not lead to a greater reduction in depressive symptoms or anxiety in 12 months following hospital discharge. The integrated care did not reduce MAEs and other secondary outcomes except for secondary prevention medication use, which increased significantly at 12 months.

These findings contrast with several previous reports[14,31–35] in which coordinated care reduced post-ACS depression symptoms. In an early multicentre randomised trial targeting patients with depression and or low social support, the ENRICHD trial found that interventions based on cognitive-behavioral therapy (CBT) were more effective in improving depressive symptoms compared to education and usual care, although the intervention did not impact clinical outcomes.[22] Several subsequent studies involving post-ACS[31,32] or post-CABG patients[34] showed that CBT and problem-solving interventions reduced depressive symptoms compared to usual care. However, these studies were conducted exclusively in cardiac patients

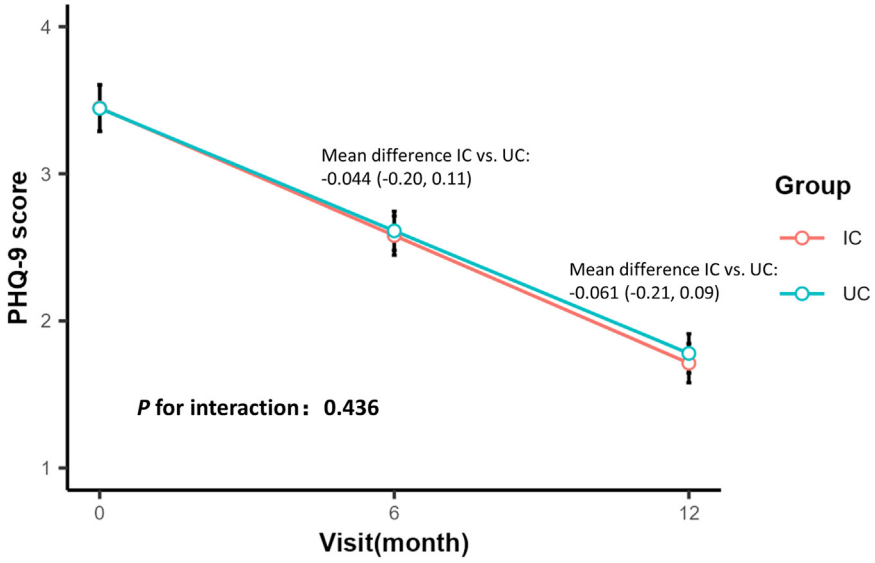

Fig. 2: Changes in depressive symptoms assessed by PHQ-9 by treatment group during follow-up. The interaction between time and treatment group was found to be non-significant (p = 0.436). The mean difference in changes in PHQ-9 score from baseline to 6- and 12-month between groups (IC vs UC) were reported separately.

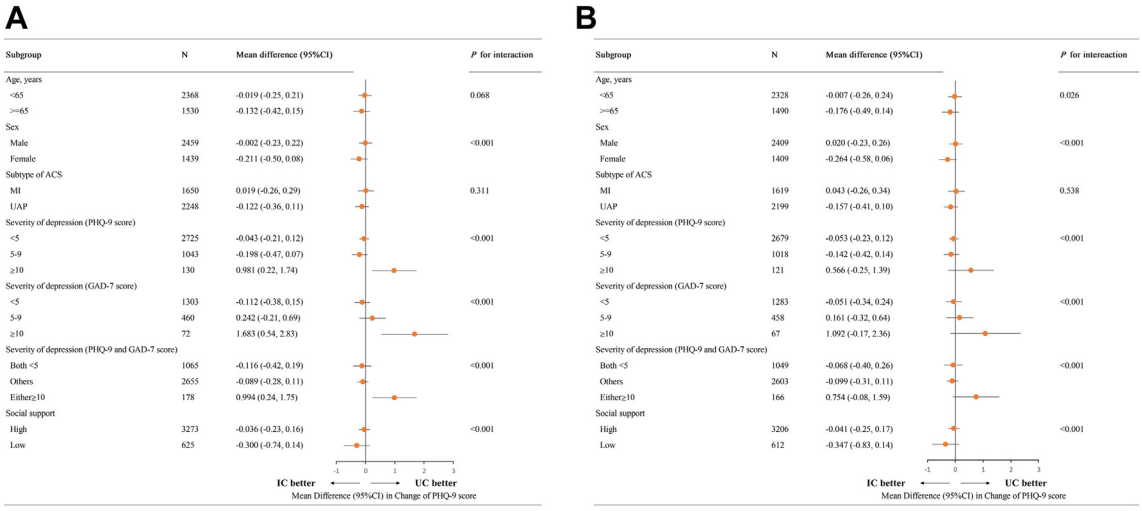

Fig. 3: Mean (95% CI) group differences in the change in PHQ-9 scores at 6-month (A) and 12-month follow-up (B) by subgroup variable including age, sex, subtype of ACS, depression severity, and level of social support.

with comorbid depression. I-Care, in contrast, was a pragmatic trial that recruited unselected ACS patients. Although this approach enhanced real-world applicability and generalisability, it could dilute the impact of the intervention and posed a challenge in fully engaging participants in the intervention. The CODIACS-QoL (Comparison of Depression Interventions After Acute Coronary Syndrome: Quality of Life) study took a similar approach and also found that depression screening and treatment did not significantly improve depressive symptoms among unselected patients.[36] Unlike the CODIACS-QoL study, in which participants with ACS were recruited 2–12 months after the documentation of disease, our study recruited patients right after the stabilisation of the disease. Thus, the patients being screened out with positive depression symptoms in our study may mostly resulted from the worries of the life-threatening nature of ACS. As long as these patients recovered from ACS their depression symptoms would gone. The significant reduction in mean PHQ-9 score in control group during the 12 months of follow up in our study and the apparently not reduced mean 10-item Center for Epidemiologic Studies Depression score during the 12 months of follow up in the CODIACS-QoL study supports our hypothesis.

There are several additional factors that could explain our null findings. First, it is important to note that our study is the first conducted among Chinese adults, for whom depression symptoms often differ from patients in Europe and the United States.[37] The depression scores were unexpectedly low in this sample of ACS patients. Indeed, the average score on the PHQ-9 was 3.6, and only 3.3% of participants enrolled reported significant depressive symptoms (PHQ-9 $\geq$ 10) at baseline. The unexpected low mean PHQ-9 score at baseline may have resulted in relatively little room for improvement. There are several possible explanations for this low rate. First, Asian cardiac patients could be less likely to have depression. A recent study[38] found 6.7% Chinese adults with coexistence of CVD and depression, similar result was also found in Japanese population.[39] However, the CODIACS-QoL study in the US also had an unexpected low rate of depression (7.1%).[36] It has been reported that patients recruited in clinical trials tended to be less depressed than those in clinical practice.[40] Second, response bias may have affected self-report scores as Chinese have more stigma of psychiatry and mental illness compared to western society[41]; thus patients may have underreported their symptoms because they were in denial or deliberately minimizing their symptoms.

We also note that our study was conducted among hospitals without readily available mental health professionals, and the treatment was provided by nurses who did not have specialty training in psychiatry. Lacking experience in delivering mental health interventions may limit the ability of non-psychiatrically trained nurses in treating individuals with more severe depression. We believe that our findings suggest that it is important to better integrate mental health professionals in the routine care of medically ill patients with depression.

The results of the subgroup analyses, while exploratory, may also help to explain the null treatment effect on the primary outcome. In our study, the treatment effect varied by pre-specified baseline characteristics. In particular, the point estimate of the treatment effect was in a favourable direction for patients with mild symptoms of depression and anxiety, but in an unfavourable direction for patients with moderate or severe

	IC group			UC group			Primary model		Covariate-adjusted model[i]	
	N[a]	n	% or mean (SD)	N[a]	n	% or mean (SD)	HRs/ORs or mean difference[g] (95% CI)	p values	HRs/ORs or mean difference[j] (95% CI)	p values
All MAEs	2034	579	28.5	1976	534	27.0	1.06 (0.95, 1.20)	0.303	1.04 (0.93, 1.17)	0.490
MAEs components										
All death	2034	79	3.9	1976	76	3.9	1.00 (0.73, 1.37)	0.996	1.00 (0.73, 1.38)	0.981
Cardiac death	2034	33	1.6	1976	39	2.0	0.81 (0.51, 1.29)	0.385	0.84 (0.53, 1.33)	0.452
Non-fatal MI	2034	41	2.0	1976	38	1.9	1.04 (0.67, 1.62)	0.861	1.03 (0.66, 1.61)	0.891
Non-fatal Stroke	2034	33	1.6	1976	18	0.9	1.77 (0.99, 3.14)	0.052	1.72 (0.97, 3.06)	0.064
Re-hospitalisation	2034	485	23.8	1976	434	22.0	1.09 (0.96, 1.24)	0.183	1.07 (0.94, 1.22)	0.313
Proportion of patients with PHQ-9 < 5										
6-month	1983	1747	88.1	1915	1693	88.4	0.97 (0.76, 1.24)	0.811	0.95 (0.76, 1.20)	0.687
12-month	1947	1742	89.5	1871	1673	89.4	1.02 (0.79, 1.31)	0.908	1.01 (0.79, 1.28)	0.952
Proportion of patients with GAD-7 < 5										
6-month	1303	1122	86.1	1264	1073	84.9	1.17 (0.88, 1.58)	0.282	1.15 (0.86, 1.53)	0.338
12-month	1725	1506	87.3	1673	1460	87.3	1.01 (0.77, 1.32)	0.942	0.99 (0.76, 1.29)	0.956
Evidence-based medication use[b]										
6-month	1983	1040	52.5	1915	966	50.4	1.09 (0.93, 1.25)	0.254	1.09 (0.95, 1.26)	0.229
12-month	1946	880	45.2	1871	764	40.8	1.21 (1.05, 1.40)	0.010	1.21 (1.05,1.40)	0.008
Blood pressure under control[c]										
6-month	1693	1227	72.5	1583	1154	72.9	0.98 (0.82, 1.16)	0.770	0.97 (0.81, 1.17)	0.774
12-month	1622	1160	71.5	1559	1143	73.3	0.99 (0.76, 1.07)	0.226	0.90 (0.74, 1.08)	0.259
Healthy lifestyle[d]										
6-month	1984	263	13.3	1915	219	11.4	1.20 (0.96, 1.50)	0.109	1.41 (0.88, 2.26)	0.148
12-month	1947	236	12.1	1871	227	12.1	0.99 (0.79, 1.25)	0.952	1.01 (0.63, 1.63)	0.968
EQ5D score[e]										
6-month	1983	–	0.94 (0.12)	1915	–	0.93 (0.12)	0.01 (−0.01,0.01)	0.906	0.01 (−0.01, 0.01)	0.993
12-month	1947	–	0.94 (0.12)	1871	–	0.93 (0.12)	0.01 (−0.01, 0.01)	0.292	0.01 (−0.01, 0.01)	0.306
GAD-7 score[f]										
6-month	1303	–	2.18 (2.49)	1264	–	2.24 (2.51)	−0.06 (−0.24, 0.11)	0.471	−0.04 (−0.21, 0.13)	0.629
12-month	1725	–	2.01 (2.42)	1673	–	1.98 (2.28)	0.02 (−0.13, 0.17)	0.801	0.03 (−0.12, 0.17)	0.731
BDI-II score[g]										
6-month	602	–	3.75 (4.47)	588	–	4.00 (4.33)	−0.22 (−0.81, 0.38)	0.476	−0.14 (−0.67, 0.39)	0.608
12-month	597	–	4.15 (5.20)	582	–	4.38 (5.07)	−0.21 (−0.80, 0.39)	0.497	−0.14 (−0.68, 0.39)	0.603
PSSS score[h]										
6-month	602	–	68.9 (12.1)	588	–	68.7 (12.7)	−0.06 (−1.05, 0.93)	0.467	−0.33 (−1.23, 0.57)	0.473
12-month	597	–	70.5 (10.5)	582	–	69.9 (10.7)	0.33 (−0.67, 1.32)	0.520	0.07 (−0.84, 0.97)	0.883

Abbreviation: IC, Integrated care; UC, usual care; MAEs, Major adverse events; MI, Myocardial Infarction; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalised Anxiety Disorder-7; EQ5D, EuroQol-5D; BDI-II, Beck Depression Inventory-II; PSSS, Perceived social support scale. [a]17 patients in IC and 14 patients in UC were lost to any follow up visits and not included in analysis of any outcomes. Reasons for other missing data included limited to subsample (BDI-II and PSSS), postposed (GAD-7), not followed up face-to-face (blood pressure measurement), and unknown (rest variables). [b]The percentage of patients using any four and above drugs out of five ACS secondary medicines, which include aspirin, clopidogrel, statin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and β-blocker. [c]The percentage of patients with blood pressure <140/90 mmHg. [d]The percentage of patients with increased healthy lifestyle, which is a global measure including no smoking, no alcohol use, body mass index <24 kg/m^2 and physical activity ≥3 times/week and more than 30 min each time. [e]A higher score indicates better quality of life. [f]A higher score indicates worse anxiety symptoms. [g]A higher score indicates depressive symptoms. [h]A higher score indicates better social support. [i]Age, gender, ACS subtype, severity of depression and social support index at baseline, and baseline value of the continuous outcomes (if any) were adjusted. [j]HR was reported for MAE outcomes; OR was reported for outcomes including the proportion of patients with PHQ-9 < 5, the proportion of patients with GAD-7 < 5, evidence-based medication use, blood pressure under control, and healthy lifestyle; mean difference was reported for EQ5D score, GAD-7 score, BDI-II score, and PSSS score.

Table 3: **Effects on secondary outcomes.**

depression or anxiety symptoms (either PHQ-9 score or GAD-7 score ≥10). There is indeed growing evidence that the presence of comorbid anxiety and depression can attenuate the benefits of treatment.[42] Furthermore, the treatment effect on secondary prevention medication use at 12 months showed a similar pattern to that on the primary outcome, i.e. the point estimate was unfavourable for IC in patients with baseline PHQ-9 score ≥10 and more favourable in patients with baseline PHQ-9 score <10. Nonetheless, caution is warranted in interpreting subgroup analyses, especially considering the small number of patients with depression defined by a PHQ-9 score ≥10.

Our results in subgroup analysis also suggested that shifting the depression care from psychiatry to non-psychiatry might need to consider right patients for the

intervention. Although exploratory, the greater beneficial effects in women, older patients, patients with low social support as well as in patients with mild depression symptoms are explainable and consistent with previous studies that showed that men and young people were less compliant to health interventions.[43,44] Also, more intensive training should be provided to ensure the technical capability of the non-specialty interventionists.

Our study found that IC did not reduce the incidence of MAEs, which is consistent with other intervention trials of depressed ACS patients.[12,14] However, we should note that the IC effectively increased secondary prevention medication use at 12 months, though the magnitude of the incremental effect was small and did not translated into benefits in clinical outcomes.

Limitations

First, participants were enrolled from rural county hospitals with no PCI facilities and our results may not be generalisable to other settings. Second, the prevalence of clinical depression and the average PHQ-9 score in our study sample were lower than expected, which raised concerns about the validity of the self-report measure and significantly lowered the power of the study. Third, we did not adjust for multiple tests in our analysis. Hence results on secondary outcomes and subgroup analyses should be considered exploratory.

Important strengths of this trial also should be noted. To our knowledge, it is the largest trial to date test the effect of an integrated care in resource-limited clinical settings. Clinical end points were adjudicated by an independent committee and the study process was closely monitored by a quality control team with 0.7% participants lost to follow-up.

Conclusions

Implementing a cardiology nurse-coordinated ACS and depression integrated care treatment in low psychiatry resource settings did not reduce depressive symptoms or improve clinical outcomes compared to usual care controls among unselected patients discharged with ACS. Greater benefits in certain subgroups warrants further studies.

Contributors

YW, XY, SL and JAB developed the research idea and designed the study. YW and XY acquired the funding. YW, SL and YZ were involved in the day-to-day management and implementation of the trial. CS, RJ, SN and GG provided technical training and oversight for the conduct of the trial. YZ performed and XL verified data analysis. PG advised on the statistical plan and analyses. YZ drafted the manuscript with input from YW and CS. JAB, XY, PKM, LLY, AP and RG critically revised the paper. All authors contributed to refinement of and approved the submitted manuscript. YW had right to access to raw data and is responsible for the decision to submit for publication.

Data sharing statement

The de-identified participant data on which this report is based will be made available, following publication, upon request to wuyf@bjmu.edu.cn, and after a signed data access agreement with the principal investigator.

Declaration of interests

YW and XY reports grants from the National Institute of Mental Health during the conduct of the study. All remaining authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101126.

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