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Collaborative care for comorbid depression and coronary heart disease: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objectives: To systematically review the efficacy of collaborative care (CC) for depression in adults with coronary heart disease (CHD) and depression.

Design: Systematic review and meta-analysis.

Data sources: Electronic databases (Cochrane Central Register of Controlled Trials MEDLINE, EMBASE, PsycINFO and CINAHL) were searched until April 2014.

Inclusion criteria: Population, depression comorbid with CHD; intervention, randomised controlled trial (RCT) of CC; comparison, either usual care, wait-list control group or no further treatment; and outcome, (primary) major adverse cardiac events (MACE), (secondary) standardised measure of depression, anxiety, quality of life (QOL) and cost-effectiveness.

Data extraction and analysis: RevMan V.5.3 was used to synthesise the data as risk ratios (RRs), ORs and standardised mean differences (SMD) with 95% CIs in random effect models.

Results: Six RCTs met the inclusion criteria and comprised 655 participants randomised to CC and 629 participants randomised to the control group (total 1284). Collaborative depression care led to a significant reduction in MACE in the short term (three trials, RR 0.54; 95% CI 0.31 to 0.95, p=0.03) that was not sustained in the longer term. Small reductions in depressive symptoms were evident in the short term (6 trials, pooled SMD −0.31; 95% CI −0.43 to −0.19, p<0.00001) and depression remission was more likely to be achieved with CC (5 trials, OR 1.77; 95% CI 1.28 to 2.44, p=0.0005). Likewise, a significant effect was observed for anxiety symptoms (SMD −0.36) and mental QOL (SMD 0.24). The timing of the intervention was a source of between-group heterogeneity for depression symptoms (between groups p=0.04, I^2=76.5%).

Conclusions: Collaborative depression care did not lead to a sustained reduction in the primary MACE end point. Small effects were observed for depression, depression remission, anxiety and mental QOL.

Trials registration number: PROSPERO CRD42014013653.

Strengths and limitations of this study

- Systematic review of randomised controlled trials and a priori defined primary and secondary outcomes.
- Exhaustive literature search and additional unpublished data provided by 5 of 6 trials.
- GRADE rating of strength of evidence as moderate.
- Heterogeneity observed between studies.
- Few studies performed outside of the USA.
- Insufficient healthcare cost data.

INTRODUCTION

Depression is widely reported to lead to an adverse coronary heart disease (CHD) prognosis,[1 2] poorer quality of life (QOL)[3 4] and high healthcare costs.[5] Despite ongoing efforts to better identify and treat depression,[6] prior psychological and pharmacological interventions designed especially for the CHD population have reported markedly lower effect sizes than has been observed among other chronic diseases such as diabetes.[7 8] Moreover, large trials such as the landmark Enhancing Recovery in CHD (ENRICHD) study[9] did not lead to a significant reduction in major adverse cardiac events (MACE), raising questions about the design[10] and acceptability[11] of depression interventions in the population with CHD.

Collaborative care (CC) is emerging as a promising model of healthcare among populations with complex mental health needs[12] and mental disorders comorbid with chronic diseases including diabetes and CHD.[13 14] CC is defined by a multiprofessional approach to patient care delivered by a primary care physician (PCP) and at least one other health professional, involving a structured patient management plan and interventions, scheduled patient follow-ups, and enhanced interprofessional communication between the multiprofessional teams.[13] Prior systematic reviews have not reported on the efficacy of CHD studies in particular,[15 16] although mixed CHD and diabetes samples

are commonplace.[13] Several large prospective randomised controlled trials (RCTs) of CC versus usual care have been reported recently,[17–19] making it feasible to examine the efficacy and early benefits of CC, which might in turn assist in the design of subsequent trials and inform clinical practice. This systematic review extends beyond previous studies by reporting the efficacy of CC for depression in adults with comorbid depression and CHD.[20]

METHODS

Search strategy

This review conformed to the PRISMA guidelines[21] and a protocol has been published elsewhere.[20] Electronic databases were searched without language restrictions until April 2014: the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. The search string exploded the topics CHD, depression and RCT, as reported previously.[20] Hand searching reference lists of articles selected for full text supplemented electronic searches. The principal investigators of studies were contacted to ascertain unpublished data and their knowledge of any other CC trials not included in our primary search. Additional data were provided for five trials[17 18 22–24] and no response was received from the TrueBlue study authors.[19]

Inclusion criteria

Population: RCT studies were performed among adults (18 years and older) with comorbid depression and CHD. Depression was defined as depression disorder or clinical depression assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) by a standardised interview (eg, Structured Clinical Interview, Composite International Diagnostic Interview) or a validated self-reports or rating scales with specific cut-off points for depression. Mixed samples (eg, heart failure, arrhythmia, diabetes) were eligible if ≥50% of the sample had a CHD diagnosis.

Intervention: CC intervention is defined as a coordinated model of care involving multidisciplinary healthcare providers, including: (1) at least one health professional (eg, nurse, psychiatrist, psychologist) in addition to the PCP; (2) a structured patient management plan that delivers either a pharmacological or a non-pharmacological depression intervention; (3) scheduled patient follow-up and (4) enhanced interprofessional communication between the multiprofessional team. CC may include usual CHD care or blended depression-CHD care.

Comparison: control group was defined as either (enhanced) usual care, wait-list control (WLS) group or no further treatment for comorbid depression-CHD.

Outcomes: primary; all-cause and CHD-related mortality as well as MACE (eg, subsequent myocardial infarction (MI), coronary revascularisation procedure, incident heart failure (HF), stroke).

Secondary: secondary outcomes include depression, anxiety and QOL (measured either dimensionally or categorically) following the intervention assessed by validated self-report questionnaires or standardised interviews. In addition, we considered economic evaluations of healthcare costs or resource utilisation including cost-effectiveness (incremental cost-effectiveness ratio) and cost-utility (quality-adjusted life years).

Study selection process, risk of bias and assessment

Two reviewers (PJT and HB) independently screened abstracts and articles for eligibility. In the case of title/abstract disagreements, the study was subjected to full-text review and disagreements were resolved by discussion. Two reviewers (PJT and HB) independently assessed included studies using the Cochrane Collaboration's tool for assessing risk of bias.[25] The tool covers sequence generation, allocation concealment, selective outcome reporting and other sources of bias. Adjudication of the strength of evidence for each end point was made according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria with GRADE Profiler 3.6.1.[26]

Synthesis of data and summary measures

Standardised mean differences (SMD) for continuous variables, risk ratios (RR) for MACE and ORs for dichotomous end points are reported with 95% CI. Data were pooled together with random effects models using the inverse-variance method.[25 27] To evaluate the presence of publication bias, the funnel plot was inspected. All analyses were performed with RevMan V.5.3.

RESULTS

The search yielded 1755 citations from which 46 articles were reviewed in detail, and 16 papers were retained which reported on 6 RCTs (figure 1). Five CC trials performed with diabetes and CHD or mixed chronic disease populations were excluded as they did not meet the threshold of more than 50% of patients with CHD.[13 28–31] Two trials were close to meeting the definition of CC for depression comorbid with CHD, but were excluded. The Identifying Depression as a Comorbid Condition (IDACC)[32] study was excluded as the intervention did not initiate pharmacological or non-pharmacological depression treatment and did not involve structured follow-up of participants to augment treatment if necessary. The UPBEAT-UK study[33] was excluded as the intervention was a case-management intervention and did not incorporate other healthcare professionals such as the PCP.

The 6 RCTs that met the inclusion criteria comprised a total of 1284 patients with comorbid depression and CHD: 655 participants randomised to CC and 629 participants randomised to a control group. A description of

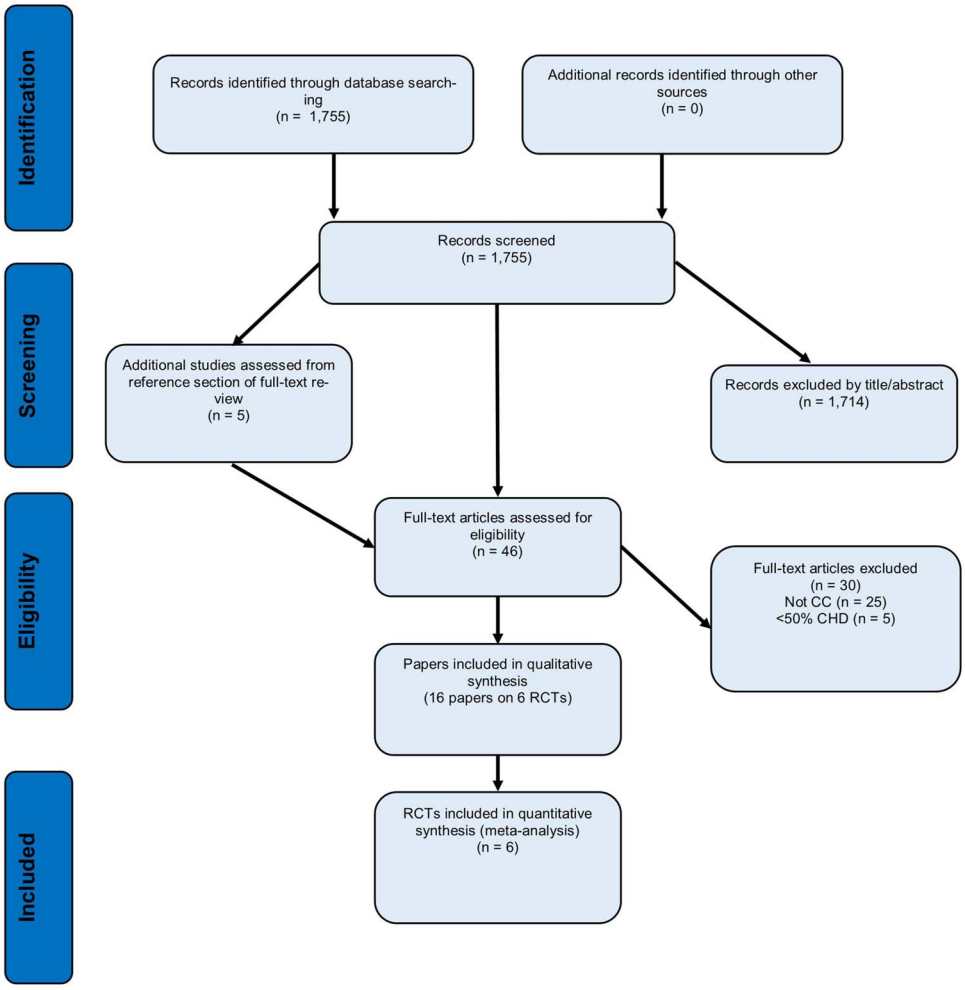

Figure 1 Flow chart of article selection (CC, collaborative care; CHD, coronary heart disease; RCT, randomised controlled trial).

the included trials is shown in table 1. The median proportion of participants with CHD in the trials was 78.9%, suggesting a high representative sampling of the chronic disease understudy. The median sample size was 179 participants per study with a median of 47.6% female participants. Four trials recruited participants from multiple sites[11 34–36] and two trials were performed at a single centre.[17 37] Five trials were from the USA[17 18 22–24] and one trial was performed in Australia.[19] The comparison group was usual care or enhanced usual care in five studies consisting of informing participants' PCP[17 18 22–24] and one trial used a WLC group.[36]

Depression screening questionnaires varied only minimally. Depression was assessed with the Patient Health Questionnaire (PHQ) to determine study eligibility in four trials.[17 19 23 24] Specifically, three trials used a two-step screening approach with the PHQ-2 and a PHQ-9 for participants with an initial positive depression response on the PHQ-2.[17 35 37] These trials used a moderate depression threshold consisting of PHQ-9 total scores ≥10.[17 35 37] The TrueBlue study[36] included patients with mild depression symptoms consisting of PHQ-9 scores ≥5. In the Coronary Psychosocial Evaluation Studies (COPES) and Comparison of Depression Interventions after Acute Coronary Syndrome (CODIACS) trials, the Beck Depression Inventory (BDI) was used for screening and trial eligibility.[11 34] The clinical cut-off was set at ≥10 on at least two different screening occasions in COPES.[11] In CODIACS,[34] the clinical cut-off was set at BDI ≥10 on at least two different screening occasions or BDI ≥15 on one occasion. Five of the trials utilising either the PHQ-9[17 36 37] or BDI[11 34] to determine trial eligibility also used the same measure for depression symptom response at the conclusion of the trial. The Bypassing the Blues trial employed the Hamilton Rating Scale for Depression[24] for depression symptom clinical response.

CC was managed by an allied health team in two trials,[11 34] by nurses in two studies[35 36] and by social workers in two studies.[17 37] The CC intervention duration ranged from 3 to 12 months and the median duration was 6 months. The psychotherapy component of the CC package consisted of problem-solving therapy in two studies,[11 34] telephone-delivered manualised CBT in one study,[37] referral to community mental health services in two studies,[35 36] and was mixed in another study.[17] The pharmacological component of the trials varied. In Bypassing the Blues,[35] depression pharmacotherapy consisted of citalopram, serotonin norepinephrine reuptake inhibitor (SNRI) or bupropion. In

Table 1 Characteristics of included CC studies in the treatment of comorbid depression and CHD

Study, country	Design and intervention length	CHD population (% CHD in total sample)	Sample size of CC vs UC (% females in total sample)	Depression assessment	CC intervention	Control group
Bypassing the Blues, Rollman *et al*, USA[24 35 40]	Single-blind effectiveness RCT, 8 months	CABG (100%)	150 CC vs 152 UC (41.4)	PHQ-2 positive screen as an inpatient and PHQ-9 score ≥10 2 weeks post-CABG, PRIME-MD for mood disorders	Structured telephone follow-up, patient preferences for depression care, psychoeducation, bibliotherapy, promoting adherence and initiation or adjustment of antidepressant pharmacotherapy provided by PCP (citalopram, SNRI or bupropion); referral to a community MHS; a combination of the above; 'watchful-waiting'	Usual care, given brochure on depression and heart disease; PCP informed of depression status
CODIACS, Davidson *et al*, USA[18 34]	Single-blind effectiveness RCT, 6 months	UA, MI (100%)	73 CC vs 77 UC (42.0)	BDI-I score ≥10 on 2 screening occasions or ≥15 on 1 occasion 2–6 months after hospitalisation	Initial patient preference for problem-solving therapy and/or pharmacotherapy (sertraline, citalopram, bupropion), or neither; then a stepped-care approach every 6–8 weeks, structured follow-up initially every week with PST or 1–2 and 3–5 weeks to titrate doses with pharmacotherapy; study team included a site physician and fed back information to PCP	Usual care, locally administered, ad libitum depression care; PCP informed of depression status
COPES, Davidson *et al*, USA[11 22 38 39 49]	Single-blind effectiveness RCT, 6 months	UA, MI (100%)	80 CC vs 77 UC (53.5)	BDI-I score ≥10 on 2 screening occasions 1 week and 3 months after hospitalisation	Initial patient preference for problem-solving therapy and/or pharmacotherapy (sertraline, escitalopram, venlafaxine, bupropion, mirtazapine), then a stepped-care approach, repeated assessments and augmentation if required at 8 week intervals, structured follow-up initially every week with PST or 1–2 and 3–5 weeks to titrate doses with pharmacotherapy, study team included a site physician and fed back information to PCP	Usual care, locally administered, ad libitum depression care; PCP informed of depression status
MOSAIC, Huffman *et al*, USA[23 37]	Single-blind effectiveness RCT, 6 months	UA, MI, HF, arrhythmia (51%)	92 CC vs 91 EUC (53.0)	Two-step screening process; PHQ-2, GAD-2 and item about panic	Social worker and psychiatrist developed individualised treatment recommendations; patient preference	Enhanced usual care; PCP informed of psychiatric status at

Continued

Table 1 Continued

Study, country	Design and intervention length	CHD population (% CHD in total sample)	Sample size of CC vs UC (% females in total sample)	Depression assessment	CC intervention	Control group
				attacks as an inpatient and PRIME-MD for depression, GAD and PD	for pharmacotherapy (SSRI most commonly citalopram, SNRI, bupropion, mirtazapine and anxiety treatment with SSRI or benzodiazepine) or CBT (minimum 6 session CBT when allocated); stepped-care; PCP informed of patient preference; structured telephone call and follow-up to monitor symptoms, promote adherence and engagement	baseline and subsequent screening
SUCCEED, Huffman *et al*, USA[17 50]	Single-blind effectiveness RCT, 3 months	UA, MI, HF, arrhythmia (52.6%)	90 CC vs 85 UC (48.6)	Two-step screening process; PHQ-2 positive screen and PHQ-9 score ≥10 as an inpatient	Social worker and psychiatrist individualised depression treatment recommendations based on history and patient preference (SSRI or psychotherapy); study team provided the PCP or cardiologist with treatment recommendations; verbal and written recommendations to the inpatient treatment team; depression education for pleasant activities scheduling; monitored for adequate depression response	Usual care; PCP informed of depression status
TrueBlue, Morgan *et al*, Australia[19 36]	Cluster randomised RCT, 12 months	CHD and diabetes (57.8)	170 CC vs 147 WLC (46.7)	PHQ-9 score ≥5 as a primary care patient	Scheduled visits to PN and PCP every 3 months over 12-months; referrals to MHS; development and recording of patient goals	Usual care; PN monitor depression by screening at scheduled intervals

BDI-I, Beck Depression Inventory-I; CABG, coronary artery bypass graft; CBT; cognitive–behavioural therapy; CC, collaborative care; CHD, coronary heart disease; CODIACS, Comparison of Depression Interventions after Acute Coronary Syndrome (Centralized, Stepped, Patient Preference-Based Treatment for Patients With Post-Acute Coronary Syndrome Depression); COPES, Coronary Psychosocial Evaluation Studies; GAD, generalised anxiety disorder; HF, heart failure; MHS, mental health services; MI, myocardial infarction; MOSAIC, Management of Sadness and Anxiety in Cardiology; PCP, primary care physician; PD, panic disorder; PHQ, Patient Health Questionnaire; PN, practice nurse; PRIME-MD, Primary Care Evaluation of Mental Disorders; PST, problem-solving therapy; RCT, randomised controlled trial; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors; SUCCEED, Screening Utilization and CC for More Effective and Efficient Treatment of Depression; UA, unstable angina; UC, usual care; WLC, wait-list control.

CODIACS,[34] depression pharmacotherapy consisted of sertraline, citalopram or bupropion. In COPES,[11] pharmacotherapy consisted of sertraline, escitalopram, venlafaxine, bupropion and mirtazipine. In Management of Sadness and Anxiety in Cardiology (MOSAIC),[37] depression pharmacotherapy consisted of selective serotonin reuptake inhibitor (SSRI, most commonly citalopram), SNRI, bupropion, mirtazapine and anxiety treatment with SSRI or benzodiazepine. In Screening Utilization and CC for More Effective and Efficient Treatment of Depression (SUCCEED),[17] depression pharmacotherapy consisted of SSRI. No specific depression pharmacotherapy regimen was reported in TrueBlue.[36]

Risk of bias

Risk of bias varied in the included primary trials (see eSupplement 1). Missing trial characteristics were common despite all studies having published a trial protocol. In four trials, the allocation concealment was unclear. Blinding to subjective end points was rated as high in all studies. Selective reporting was noted in three studies because of discrepancies in the study end points reported in the protocol in comparison with the primary trial results.

Primary outcome: major adverse cardiac events

Three trials reported MACE[18 24 38] and pooling all data irrespective of follow-up showed that CC did not reduce MACE (RR=0.87; 95% CI 0.53 to 1.42, p=0.20, I^2=39%). CC was associated with significant reduction in MACE during the short to medium term (RR=0.54; 95% CI 0.31 to 0.95, p=0.03) that was not sustained in the long term (>12 months follow-up) where only the COPES trial[39] reported MACE (RR 1.04; 95% CI 0.51 to 2.14, p=0.91) (figure 2). There was no association with mortality (5 trials, RR 1.38; 95% CI 0.53 to 3.58, p=0.51).

Secondary outcomes

Depression symptoms and remission

All six trials reported a change in self-reported depression symptoms by 6 months postintervention. CC was associated with a significant reduction in depressive symptoms (pooled SMD −0.31; 95% CI −0.43 to −0.19, p<0.00001: I^2=13%) (figure 3). There was no depression symptom data available in the medium or long term. Four trials reported depression remission or clinically significant depression response and additional data were provided by the MOSAIC trial.[23] CC was significantly associated with depression remission (OR=1.77; 95% CI 1.28 to 2.44, p=0.0005: I^2=23%) (figure 4). In the medium term, only the COPES trial[39] reported depression response based on the BDI ≤10 (OR 2.26; 95% CI 1.14 to 4.46, p=0.02). Since the COPES trial[39] reported similar depression remission results in the short to medium term, pooling all depression remission data in the five trials, irrespective of the time frame, indicated similar results.

Other secondary outcomes

The forest plots for each of the secondary end points are reported in eSupplements 2 to 5. Four trials reported anxiety symptom change. It was found that CC led to a small, but significant reduction in anxiety symptoms in the short term (SMD −0.36; 95% CI −0.54 to −0.17, p=0.0001: I^2=25%). CC was also associated with a significant improvement in mental QOL in the short term across five trials (SMD 0.23; 95% CI 0.08 to 0.38, p=0.003: I^2=27%), while effects for physical QOL were non-significant (SMD 0.11; 95% CI −0.03 to 0.25, p=0.12: I^2=13%). In terms of cost-effectiveness, there was

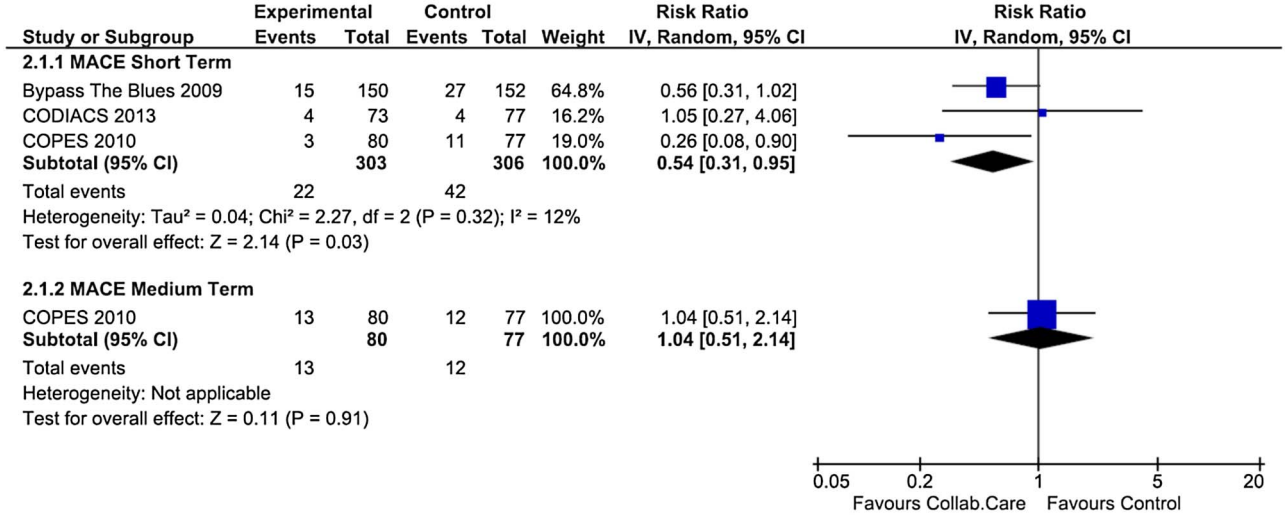

Figure 2 Forest plot showing the risk ratio for MACE postintervention in collaborative care studies versus usual care or waiting list control (short and medium terms). MACE, major adverse cardiac events; IV, inverse variance; CODIACS, Comparison of Depression Interventions after Acute Coronary Syndrome; COPES, Coronary Psychosocial Evaluation Studies.

for anxiety symptom reduction and improvement in mental QOL were evident with CC. However, it remains to be shown that collaborative depression care can lead to sustained reductions in cardiovascular events and a moderate depression response in the longer term. Scant RCT data exist outside of the USA and the cost-effectiveness has not been established at this time.

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