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Healthcare provider-led interventions to support medication adherence following ACS: a meta-analysis

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ABSTRACT

We conducted a systematic review and meta-analysis to determine the effectiveness of healthcare provider-led (HCPs) interventions to support medication adherence in patients with acute coronary syndrome (ACS). A systematic search of Cochrane Library, Medline, EMBASE, PsycINFO, Web of Science, IPA, CINAHL, ASSIA, OpenGrey, EthOS, WorldCat and PQDT was undertaken. Interventions were deemed eligible if they included adult ACS patients, were HCP-led, measured medication adherence and randomised participants to parallel groups. Intervention content was coded using the Behaviour Change Technique (BCT) Taxonomy and data were pooled for analysis using random-effects models. Our search identified 8870 records, of which 27 were eligible (23 primary studies). A meta-analysis (n=9735) revealed HCP-led interventions increased the odds of medication adherence by 54% compared to control interventions (k=23, OR 1.54, 95% CI 1.26 to 1.88, I^2=57.5%). After removing outliers, there was a 41% increase in the odds of medication adherence with moderate heterogeneity (k=21, OR 1.41, 95% CI 1.21 to 1.65, I^2=35.3%). Interventions that included phone contact yielded (k=12, OR 1.63, 95% CI 1.25 to 2.12, I^2=32.0%) a larger effect compared to those delivered exclusively in person. A total of 32/93 BCTs were identified across interventions (mean=4.7, SD=2.2) with 'information about health consequences' (BCT 5.1) (19/23) the most common. HCP-led interventions for ACS patients appear to have a small positive impact on medication adherence. While we were able to identify BCTs among interventions, data were insufficient to determine the impact of particular BCTs on study effectiveness.

PROSPERO registration number CRD42016037706.

INTRODUCTION

Pharmacological therapy is a key component of secondary prevention following acute coronary syndrome (ACS). Despite the effectiveness of such therapies, many patients do not follow their regimen as prescribed and are deemed non-adherent. It is estimated that approximately one-third of patients are non-adherent to cardiac medications following ACS.[1] Non-adherence among cardiac patients presents a considerable clinical problem because of its association with poor outcomes that include mortality, morbidity and risk of rehospitalisation.[2]

Adherence is complex in nature and is driven by a myriad of patient-related (eg, beliefs about treatment), healthcare provider (HCP)-related (eg, communication) and healthcare system-wide factors (eg, treatment cost and access). A recent review of psychosocial factors found that depression and treatment beliefs were predictors of non-adherence following ACS.[3] Identifying potentially modifiable factors is crucial for the design and implementation of evidence-based interventions to improve adherence.

There have been multiple attempts to synthesis the evidence base for adherence interventions in chronic disease,[4] coronary artery disease (CAD)[5] and cardiovascular disease.[6] Moreover, there have been numerous reviews looking at interventions targeting adherence to specific medication classes including statins,[7] antihypertensives[8] and oral antiplatelet therapy.[9] HCPs (ie, physicians, nurses, pharmacists) play a key role in supporting, promoting and monitoring adherence for chronic conditions. Previous reviews have reported the benefit of adherence interventions delivered by multiple HCPs,[10] pharmacists[11] and nurses.[5] However, to date, the impact of these types of interventions for patients with ACS has yet to be systematically explored.

Interventions that target behaviours such as medication taking are often complex and comprise multiple components. In order to identify the specific strategies best suited to change specific behaviours, complex interventions need to be compartmentalised. Behaviour change frameworks such as the theoretical domains framework[12] and behaviour change technique (BCT) taxonomy[13] have been designed to aid this compartmentalisation process through specifying interventions into their 'active content'. These types of models have been used across

a range of health behaviours, and there is increasing application within medication adherence research.[14]

The primary objective of this systematic review and meta-analysis is to determine the effectiveness of HCP-led interventions to support medication adherence following ACS. Additionally, we aim to examine whether effectiveness is moderated by interventionist, delivery method and having a theory-based design. Finally, we aim use a behaviour change framework to identify the specific techniques used among adherence interventions.

METHODOLOGY

This review was conducted in accordance of the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines[15] and was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016037706).

Eligibility criteria

Studies were included if they met the following criteria:

1. Participants: adults (>18 years of age) with a confirmed diagnosis of ACS.
2. Intervention: delivered by HCPs.
3. Comparator: parallel group design where treatment group is compared with a clearly defined control group.
4. Outcome: include a measurement or medication adherence as a primary or secondary outcome.
5. Setting: study group allocation determined by randomisation.

We defined an intervention as being HCP led if the primary method of delivery involved HCPs working therapeutically with patients in person and/or via phone.

Studies infrequently distinguish between the different types of non-adherence; therefore, we used a definition of medication adherence that includes treatment initiation, actual dosing and treatment persistence.[16]

Search strategy

A systematic search of the following electronic databases was conducted: The Cochrane Library, Medline, EMBASE, PsycINFO, Web of Science, International Pharmaceutical Abstracts, Cumulative Index to Nursing and Allied Health Literature and Applied Social Sciences Index and Abstracts. An additional grey literature search was also undertaken: OpenGrey, EthOS, WorldCat—Thesis and Dissertations and ProQuest Dissertations & Theses. Searches were limited to articles written in English with no timespan limits. Reference lists of relevant papers were also searched to identify any additional records.

Our search strategy was informed by previous review studies[4 5] and comprised four search themes: condition; therapy type; adherence; study design (see table 1) (for full search strategy, see online supplementary material 1).

Table 1 Search themes with example search terms

Search theme	Examples of search terms
Condition	Acute coronary syndrome, myocardial infarction, unstable angina, coronary occlusion, coronary thrombosis
Therapy type	Treatment, medication, medicine, drug, pharmacotherapy, regimen, prescription, prescribed
Adherence	Compliance, non-compliance, concordance, adherence, non-adherence, discordance, persistence, non-persistence, discontinuation, drop-out, treatment refusal
Study design	Random, clinical, control, trial, intervention, outcome, treatment outcome

Data extraction

Records were imported into bibliographic software (EndNote X7) where duplicates were removed. All records were initially screened based on their title and abstract, and relevant articles were full-text screened using our eligibility criteria. All screening and data extraction was undertaken by a single researcher (JC) with experience conducting evidence syntheses. Two additional researchers (VA & JW) undertook partial screening using the eligibility criteria to validate the study selection and data extraction process. Any disagreements between raters (JC, VA and JW) were resolved by consensus. Data were extracted using a standardised data extraction form based on previous review studies[4 5 17] (see table 2). Where necessary, study authors were contacted directly for additional information. We contacted 10 authors to clarify aspects of their methodology of which 80% responded.

Risk of bias

Methodological quality was judged using A Cochrane Risk of Bias Assessment Tool (ACROBAT)[18] where risk is rated as 'high', 'unclear' or 'low' among six domains of bias (Selection; Performance; Detection; Attrition;

Table 2 Data extraction criteria

Data category	Specific extraction
Study details	Author; title
Source attributes	Study type; funding details; year of distribution
Methodological features	Group assignment; allocation concealment; comparator group; blinding; attrition; intention to treat; study period; outcome measurement
Participant characteristics	Age; gender; ethnicity; diagnosis
Intervention features	Number of sessions; interventionist; length of delivery; theoretical basis; delivery method; targeting additional health behaviours
Intervention content	BCTs
Effect size determinations	Sample size; methods of analysis; means; main effects

BCTs, behaviour change technique.

Reporting and Other Biases). ACROBAT has been used in previous systematic reviews looking at the effectiveness of adherence interventions.[19] Risk of bias was assessed by a single researcher (JC).

Statistical analysis

Medication adherence was our target outcome, and the direction of effect was transformed for consistent reporting. Where studies reported adherence across multiple medications the data were pooled to provide an estimate of 'overall adherence'. Effect size estimates are expressed in terms of ORs. Where data were originally expressed as means, standardised mean differences were calculated and then transformed to the OR metric using the probit method.[20] These should be interpreted as standardised OR.

Random-effects models comparing HCP-led interventions with control interventions were used based on the assumption that there would be statistical heterogeneity from pooling primary study data. The I^2 statistic was used to estimate statistical heterogeneity, and Cochrane guidelines were used for interpretation.[21] Potential publication bias was determined using funnel plots and Egger's test for small study effects. A critical value of. 1 was used for heterogeneity and small study effects significance testing. A study was deemed to be an outlier where the effect size was outside the pseudo 95% CI in the funnel plot as a means for detecting the potential impact of outliers on the pooled effect size.

Secondary studies (ie, primary study data with alternate end-points) were excluded from meta-analysis so as not to duplicate data. Prespecified subgroup analyses were conducted based on (1) type of interventionist, (2) delivery method and (3) theory-based design. Additional post hoc analyses were done based on adherence outcome and risk of bias. All analyses were done using Stata 14.1.

Coding intervention content

We used the BCT taxonomy[13] to identify specific techniques used to change medication-taking behaviour among our intervention studies. The BCT taxonomy comprises 93 unique BCTs categorised into 16 clusters. A BCT is defined as an 'active ingredient' that can be used to alter or redirect behaviour. The BCT taxonomy includes a detailed description of each technique and provides specific examples (eg, 'action planning' (BCT 1.4): *'prompt planning the performance of a particular physical activity at a particular time on certain days of the week'* (the numbers in parentheses refer to the BCT's taxonomy cluster)). The BCT taxonomy has been used to code the content of interventions across a range of health behaviours including medication adherence.[14]

The BCT content of each intervention was rated by two researchers (JC and LA). Intervention data were sourced from each published manuscript and relevant supporting documents (ie, study protocols, intervention manuals). The researchers initially rated the interventions independently and then met to discuss. BCT content was scrutinised until consensus was met between researchers.

RESULTS

Selection process

Our comprehensive search strategy identified 6072 records that were initially screened based on their title and abstract (see figure 1). A total of 5874 records were excluded, leaving 198 records to be full-text screened. Twenty-seven studies[22–48] met our eligibility criteria, which comprised 23 primary studies (4 secondary studies[37 38 43 47]) (for full reason for exclusion list, see online supplementary material). Only primary study data (k=23, n=9735) will be discussed in the following sections.

Study characteristics

Full details of the included studies can be found in table 3. The majority of interventions included nurses in their delivery (k=13[23 24 26–28 31 33 35 36 40 42 45 48]). Six interventions were led by pharmacists (k=6[22 29 30 32 41 48]), and two were delivered by physicians (k=2[25 39]). Physiotherapists,[44] problem-solving therapists[34] and community health workers[46] acted as interventionists in singular trials. Nine studies were delivered exclusively in person (k=9[24 26 27 31 34 36 39 41 48]), while 10 studies included both in person and phone contact (k=10[22 23 29 30 32 33 42 44–46]). Just four study interventions were delivered exclusively by phone (k=4[25 28 35 40]), while six included a face-to-face predischarge component (k=6[22 23 28 30 39 41]). The number of intervention sessions ranged from 1[28 32 48] to 24[26] (k=21; median=4.0, SD=6.0). A total of 10 studies followed patients up for either 6 (k=5[22 24 32 34 39]) or 12 months (k=5[29–31 46 48]) (k=23; median=6.0 months, SD=10.3 months). Adherence to medication was a primary outcome in 14 studies (k=14[22 24 28–30 32 34 36 39–42 45 46]) and was measured exclusively by self-report in 16 studies (k=16[23–28 31–34 36 39–41 44 45]). Five studies used pharmacy data or pill counts (k=5[30 35 42 46 48]), and just two studies used both self-report and pharmacy data to measure adherence (k=2[22 29]).

Risk of bias

A summary of the risk of bias assessment can be seen in figure 2. All but one of the studies[31] were rated as having 'unclear' risk of performance bias due to the impracticality of blinding participants and personnel to group allocation during behavioural studies. 'High' risk of detection bias was judged in nine studies that did not adopt end-point blinding (k=9[24 26 28 36 39 40 44 45 48]). After excluding performance bias ratings, six studies were judged to have 'low' risk of bias across all other domains (k=6[22 27 30 34 41 44]). Three of these 'low-risk' studies were delivered by pharmacists (k=3[22 30 41]), and the rest were led by nurses,[27] physiotherapists[44] or problem-solving therapists.[34] Trials with the smallest[41] and largest sample sizes[27] were among the 'low risk'-rated studies, and all six were either delivered exclusively in person (k=3[27 34 41]) or in person with phone contact (k=3[22 30 44]) (for complete

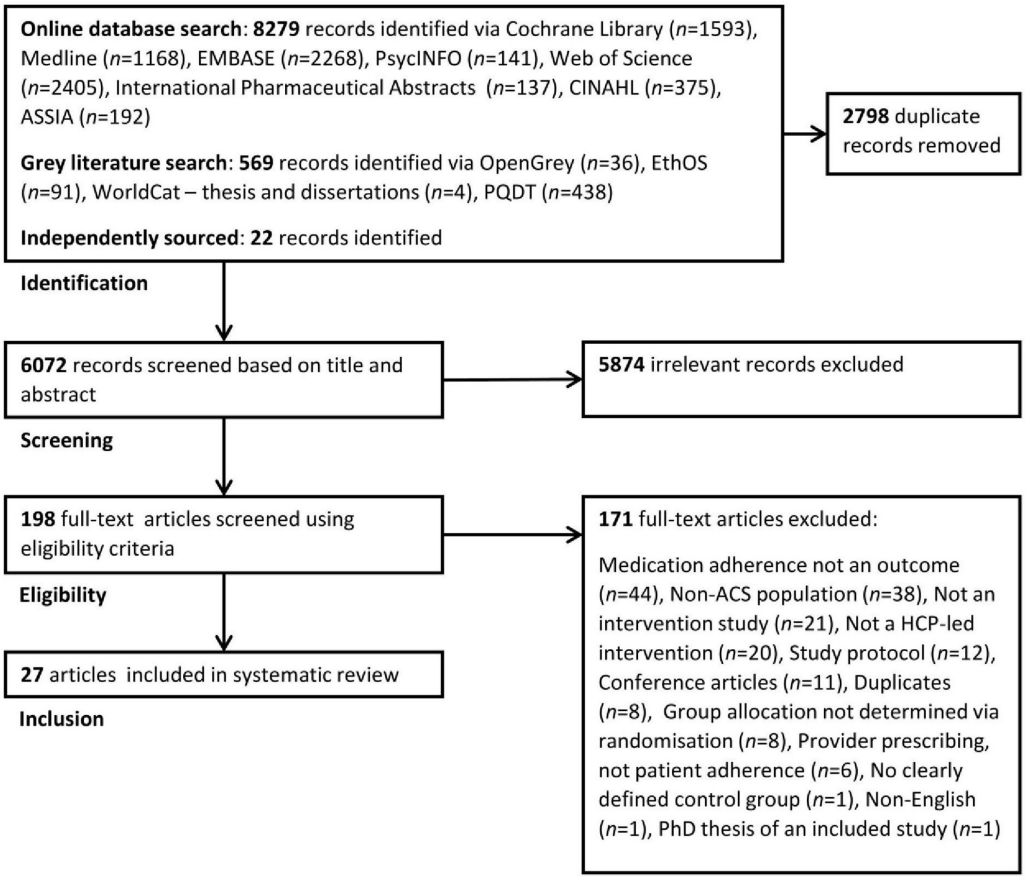

Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analysis flow diagram showing the study selection process. ACS, acute coronary syndrome; ASSIA, Applied Social Sciences Index and Abstracts; CINAHL, Cumulative Index to Nursing and Allied Health Literature; HCP, healthcare provider; PQDT, ProQuest Dissertations & Theses.

risk of bias assessment, see online supplementary material).

BCT inclusion

Figure 3 shows the frequency of BCTs coded across studies. None of the studies referenced the BCT taxonomy in their intervention design. A total of 32 (34%) of the 93 BCTs listed in the taxonomy were identified among studies, ranging between 1[28 33] and 10[44] (mean=4.7, SD=2.2). 'Information about health consequences' (BCT 5.1) was the most commonly identified BCT, coded in 19 of the 23 studies. 'Social support (unspecified)' (BCT 3.1) was coded in seven studies, and 'action planning' (BCT 1.4) was identified in just two studies.[32 44] There were six instances of 'goal setting (outcome)' (BCT 1.3), 'monitoring of behaviour by others without feedback' (BCT 2.1), 'feedback on outcome(s) of behaviour' (BCT 2.7) and 'instruction on how to perform the behaviour' (BCT 4.1) across studies. Around two-thirds (67%) of the total number of BCTs coded were from just three taxonomy clusters: goals and planning (cluster 1, n=26 (24%)), natural consequences (cluster 5, n=25 (23%)) and feedback and monitoring (cluster 2, n=21 (20%)). There were no BCTs coded from three taxonomy clusters: reward and threat (cluster 10), scheduled consequences (cluster 14) and covert learning (cluster 16). There were no instances where every BCT in a cluster was coded (goals and planning: cluster 1, 8/9 BCTs coded; feedback and monitoring: cluster 2, 6/7 BCTs coded).

Meta-analysis

A random-effects meta-analysis of 23 primary studies (n=9735) revealed that HCP-led interventions increased the odds of medication adherence by 54% compared with control interventions with moderate to high statistical heterogeneity (k=23, OR 1.54, 95% CI 1.26 to 1.88 (I^2=57.5%, P=0.001)) (see figure 4). After removing two outliers,[40 45] a meta-analysis of 9545 patients indicated that HCP-led interventions increased the odds of medication adherence by 41% compared with control interventions with moderate statistical heterogeneity (k=21, OR 1.41, 95% CI 1.21 to 1.65 (I^2=35.3%, P=0.057)) (see figure 5). While Egger's test was non-significant (P=0.286), visual inspection of the funnel plot suggests a potential bias even after discounting outliers (for funnel plot, see online supplementary material).

Subgroup analyses

Table 4 shows the results of our prespecified (ie, interventionist, delivery method, theoretical basis) and post hoc (ie, adherence outcome, risk of bias) subgroup analyses. The largest effect sizes were for interventions that

Table 3 Data extraction for all intervention studies identified in the systematic review process (k=27)

	Study details				Participant characteristics	
Author	**Year**	**Country**	**Design, setting**	**Sample size**	**Sample characteristics**	**Control group**
Calvert *et al*[22]	2012	USA	RCT, multi-site (n=2)	143	Median age: IG=63, CG=62; male: IG=66%, CG=61%; White: IG=51%, CG=51%	Usual care: routine discharge counselling and discharge summary sent to community physician.
Cossette *et al*[23]	2012	Canada	RCT, single site	242	Mean age: IG=59, CG=59; male: IG=81%, CG=90%	Usual care: received standard predischarge care. Encouraged to use regular healthcare resources postdischarge.
Costa e Silva *et al*[24]	2008	Brazil	RCT, single site	153	Mean age: IG=58, CG=59; male: IG=63%, CG=64%	Usual care: standard outpatient follow-up with a cardiologist.
Du *et al*[25]	2016	China	RCT, single site	979	Mean age: IG=60, CG=62; male: IG=73%, CG=72%	Usual care: standard follow-up with research nurse.
Giallauria *et al*[26]	2009	Italy	RCT, single site	52	Mean age: IG=58, CG=57; male: IG=85%, CG=85%	Usual care: following standard 3-month cardiac rehab, patients were discharged with usual routine recommendations and were seen only at the 12-month and 24-month follow-up.
Giannuzzi *et al*[27]	2008	Italy	RCT, multi-site (n=78)	3241	Mean age: IG=58, CG=58; male: IG=86%, CG=87%	Usual care: a letter sent to the family physician recommending secondary prevention goals followed by standard cardiac rehab and follow-up.
Gould[28]	2011	USA	RCT, single site	129	NR	Usual care: patients received routine discharge materials and usual care.
Gujral *et al*[29]	2014	Australia	RCT, single site	200	Mean age: IG=58, CG=60; male: IG=77%, CG=80%	Usual care: medication beliefs not communicated to their community pharmacist. The community pharmacists were asked to provide the patient with usual care when they collected their prescription medications.
Ho *et al*[30]	2014	USA	RCT, multi-site (n=4)	253	Mean age: IG=64, CG=64; male: IG=98%, CG=98%; White: IG=82%, CG=75%	Usual care: patients received standard ACS hospital discharge instructions, a discharge medication list and educational information about cardiac medications. A 12-month clinic visit was scheduled.
Jalal *et al*[32]	2016	UK	RCT, single site	71	Mean age=NR; male=76%	Usual care: following predischarge counselling from the hospital pharmacist, patients refilled their prescriptions at their usual pharmacies.
Jorstad *et al*[31]	2013	Netherlands	RCT, multi-site (n=11)	733	Mean age: IG=58, CG=58; male: IG=80%, CG=80%	Usual care: outpatient clinic visits to treating cardiologists and other relevant specialists. Patients were referred to cardiac rehab according to national guidelines.
Kotowycz *et al*[33]	2010	Canada	RCT, single site	54	Mean age: IG=56, CG=55; male: IG=81%, CG=70%	All discharge planning and follow-up were left to the treating physician and nursing team.

Continued

Table 3 Continued

	Study details				Participant characteristics	
Author	**Year**	**Country**	**Design, setting**	**Sample size**	**Sample characteristics**	**Control group**
Kronish *et al*[34]	2012	USA	RCT, multi-site (n=5)	177	Mean age: IG=59, CG=61; male: IG=46%, CG=47%	Usual care: treating physicians notified about their patients' depressive status. Patients given appropriate care for depressive symptoms.
Lapointe *et al*[35]	2006	Canada	RCT, single site	127	Mean age: IG=58, CG=57; male: IG=89%, CG=78%	Standard follow-up with patients' regular physician.
Miller *et al*[36]	1988	USA	RCT, multi-site (n=3)	103	Mean age=NR (range 30 - 65); male: IG=73%, CG=89%; White: IG=98%, CG=87%	Usual care: all patients had received standard inpatient cardiac rehab.
Miller *et al*[37]	1989	USA	RCT, multi-site (n=3)	81	Mean age=54; male=81%	Usual care: all patients had received standard inpatient cardiac rehab.
Miller *et al*[38]	1990	USA	RCT, multi-site (n=3)	51	Mean age=55; male=76%	Usual care: all patients had received standard inpatient cardiac rehab.
Muñiz *et al*[39]	2010	Spain	RCT, multi-site (n=64)	1757	Mean age: IG=62, CG=64; male: IG=78%, CG=76%	Usual care.
Najafi *et al*[40]	2016	Iran	RCT, single site	100	Mean age: IG=59, CG=58; male: IG=54%, CG=38%	Routine care including check-ups with designated physician.
Polack *et al*[41]	2008	Canada	RCT, single site	10	Mean age: IG=59, CG=65; male: IG=80%, CG=100%	Usual care: standard predischarge nurse education.
Polsook *et al*[42]	2016	Thailand	RCT, single site	44	Mean age: IG=61, CG=63; male: IG=86%, CG=86%	Usual care in the cardiac inpatient department that included education about patients' condition and treatment.
Redfern *et al*[44]	2008	Australia	RCT, single site	144	Mean age: IG=62, CG=67; male: IG=74%, CG=75%	Ongoing conventional care determined by patients' family physician and cardiologist.
Redfern *et al*[43]	2009	Australia	RCT, single site	144	Mean age: IG=62, CG=67; male: IG=74%, CG=75%	Usual care: received medical treatment, including pharmacotherapy and lifestyle counselling, as determined by their usual doctors.
Uysal and Ozcan[45]	2015	Turkey	RCT, multi-site (n=2)	90	Mean age=NR (47% between 45-54); male: IG=80%, CG=76%	Received home education kit comprised of brochures about healthy living post-MI. Not provided with telephone counselling and education.
Xavier *et al*[46]	2016	India	RCT, multi-site (n=14)	806	Mean age: IG=56, CG=57; male: IG=82%, CG=83%	Standard care: patients were asked to alert the research team to any hospital visits that they planned.
Sharma *et al*[47]	2016	India	RCT, single site	100	Mean age: IG=57, Con=61; Male total=84%	Usual care.
Yorio *et al*[48]	2008	USA	RCT, single site	144	Median age: IG=56, CG=56; male: IG=67%, CG=57%; White: IG=32%, CG=35%	Usual care: standard postdischarge care that included appointments with a cardiologist and family physician within 3 months.

Continued

Table 3 Continued

	Methodological features					
Author	**Intention to treat**	**Follow-up**	**Adherence as an outcome**	**Primary outcome**	**Adherence measurement**	**Sessions**
Calvert *et al*[22]	Not stated	6 months	Primary	Medication adherence	Self-report; MMAS-4; PDC	4
Cossette *et al*[23]	Not stated	6 weeks	Secondary	Cardiac rehab attendance	MMAS-4	3
Costa e Silva *et al*[24]	Yes	6 months	Primary (one of)	Clinical improvement index (including medication adherence)	Self-report	2
Du *et al*[25]	Not stated	36 months	Secondary	Mortality and MACE	MMAS-4	6
Giallauria *et al*[26]	Not stated	24 months	Secondary	Cardiopulmonary parameters and cardiovascular risk profile (including medication adherence)	Self-report	24
Giannuzzi *et al*[27]	Yes	36 months	Secondary	MACE	Self-report	11
Gould[28]	Not stated	3 days	Primary (one of)	Medication adherence, use of urgent care, patient satisfaction and illness perceptions	MMAS-4	1
Gujral *et al*[29]	Not stated	12 months	Primary (one of)	Medication adherence and treatment beliefs	MARS; MPR	2
Ho *et al*[30]	Yes	12 months	Primary	Medication adherence	PDC	4
Jalal *et al*[32]	Not stated	6 months	Primary	Medication adherence	MMAS-8	1
Jorstad *et al*[31]	Not stated	12 months	Secondary	Lifestyle and biometric targets	Self-report	4
Kotowycz *et al*[33]	Yes	6 weeks	Secondary	MACE	Self-report	4
Kronish *et al*[34]	Yes	6 months	Primary (one of)	Adherence to medication, heart healthy diet, regular exercise and smoking cessation	Self-report	NR
Lapointe *et al*[35]	Not stated	18 months	Secondary	LDL-C targets	Prescription refills	NR
Miller *et al*[36]	Not stated	60 days	Primary	MRA	HBS	3
Miller *et al*[37]	Not stated	12 months	Primary	MRA	HBS	3
Miller *et al*[38]	Not stated	24 months	Primary	MRA	HBS	3
Muñiz *et al*[39]	Not stated	6 months	Primary (one of)	Behavioural and clinical targets (including medication adherence)	Self-report	2
Najafi *et al*[40]	Not stated	3 months	Primary	Medication adherence	MMAS-8	6
Polack *et al*[41]	Not stated	6 weeks	Primary (one of)	Medication adherence and knowledge retention	MMAS-4	2
Polsook *et al*[42]	Not stated	4 weeks	Primary (one of)	Medication adherence and self-efficacy	Pill count	14
Redfern *et al*[43]	Yes	3 months	Secondary	Behavioural and clinical targets	Self-report	5
Redfern *et al*[44]	Yes	12 months	Secondary	Behavioural and clinical targets	Self-report	5
Uysal and Ozcan[45]	Not stated	3 months	Primary (one of)	Physical activity, medication adherence, anginal symptoms	MMAS-4	3
Xavier *et al*[46]	Yes	12 months	Primary	Medication adherence	CMAS	18
Sharma *et al*[47]	Yes	24 months	Primary	Mediation adherence	CMAS	10
Yorio *et al*[48]	Not stated	12 months	Secondary	Improved LDL-C profile	Prescription refills	1

Continued

Table 3 Continued

Author	Intervention features			
	Interventionist	Delivery method	Theoretical basis	Intervention summary
Calvert *et al*[22]	Pharmacist	In person and phone	Not stated	Predischarge counselling covering the importance and purpose of medications and barriers to adherence. Pocket medication card, cheat sheet (tips for remembering) and pillbox also provided. Regular follow-up with community pharmacist to discuss adherence-related issues.
Cossette *et al*[23]	Nurse	In person and phone	CS-SRM	Predischarge counselling session: symptom and physical activity management, coherence around illness episode, concerns/worries. Postdischarge counselling sessions: disease management, concerns/worries and intentions about risk factor modification, problem solving.
Costa e Silva *et al*[24]	MDT (included nurse)	In person only	Not stated	Transdisciplinary outpatient care provided. Detailed treatment planning and follow-up with nurse, dietitian, endocrinologist and cardiologist. HCPs collaborated to reinforce lifestyle change and formulate a care plan.
Du *et al*[25]	Physician (cardiologist)	Phone only	Not stated	Physician-led intensive telephone follow-up over 36 months. Patients provided with additional health education, disease-prevention suggestions and consultations on medication usage. Face-to-face visits were scheduled if necessary.
Giallauria *et al*[26]	MDT (included nurse)	In person only	Not stated	Monthly hospital meetings to discuss lifestyle change and engage in exercise training. Received a booklet about lifestyle change and promoting patients' role in their healthcare. Encouraged family support throughout.
Giannuzzi *et al*[27]	MDT (included nurse)	In person only	Not stated	Comprehensive cardiac rehab sessions that included exercise training and lifestyle and risk factor counselling. Encouraged family support throughout. Pharmacological treatments positively recommended to all patients. Received booklet to support lifestyle change and patient empowerment.
Gould[28]	Nurse	Phone only	CS-SRM	Patients received written discharge materials, telephone follow-up by an expert, medication review materials, a medication pocket card and suggested websites.
Gujral *et al*[29]	Pharmacist	In person and phone	NCF	Tailored intervention targeting treatment beliefs. Beliefs and attitudes towards treatment elicited using repertory grid technique and then communicated to the community pharmacist. Information used to tailor their discussions with the patient during follow-up. Patient also reviewed monthly by community pharmacist to discuss adherence-related issues.
Ho *et al*[30]	Pharmacist	In person and phone	Not stated	Pharmacist-led postdischarge medication reconciliation and follow-up. Predischarge and postdischarge education sessions with pharmacist followed by automated educational voice messages. Use of pill boxes to organise medications. Increased communication between pharmacists and patients' care team. Automated voice reminders to refill prescriptions.
Jalal *et al*[32]	Pharmacist	In person and phone	Not stated	Community pharmacist-led motivational interview aimed at improving protective cardiovascular medicine taking. Consultations were delivered as part of the New Medicine Service or a Medication Usage Review (established UK NHS pharmacy services).
Jorstad *et al*[31]	Nurse	In person only	Not stated	Outpatient visits with a nurse: educational sessions targeted lifestyle change and risk factor management. Lifestyle and risk factors reviewed and patients received individual counselling. Medication adherence encouraged and reasons for discontinuation discussed.

Continued

Table 3 Continued

Author	Intervention features			
	Interventionist	Delivery method	Theoretical basis	Intervention summary
Kotowycz *et al*[33]	Nurse	In person and phone	Not stated	Nurse-led patient education about the nature and management of their cardiac disease, with a focus on medications and facilitation of discharge planning.
Kronish *et al*[34]	Other (problem-solving therapist)	In person only	Not stated	Patients given a choice of either PST and/or pharmacotherapy. Weekly PST sessions were brief, problem focused and designed to augment self-efficacy and address psychosocial issues. Focus also on the initiation of pleasant activities. Patients given choice of different pharmacotherapy.
Lapointe *et al*[35]	Nurse	Phone only	Not stated	Patients received postdischarge letter and phone call concerning risk factor education and management. Clinical goals (lipid profile) set and patients received additional intervention from their physician if goals not met. Compliance assessment with pharmacist conducted at 12 and 18 months.
Miller *et al*[36]	Nurse	In person only	TRA	Intervention included an assessment (addressing attitudes, beliefs and intentions), problem identification (coping and societal adjustment) and developing a detailed health plan. Spouses were encouraged to participate.
Miller *et al*[37]	Nurse	In person only	TRA	Intervention included an assessment (addressing attitudes, beliefs and intentions), problem identification (coping and societal adjustment) and developing a detailed health plan. Spouses were encouraged to participate.
Miller *et al*[38]	Nurse	In person only	TRA	Intervention included an assessment (addressing attitudes, beliefs and intentions), problem identification (coping and societal adjustment) and developing a detailed health plan. Spouses were encouraged to participate.
Muniz *et al*[39]	Physician	In person only	Not stated	Focused on the patient-provided relationship. Discharge interview included a signed agreement of secondary prevention care plan and comprehensive written material about risk factor management. During a follow-up session, agreement reviewed and adapted if necessary.
Najafi *et al*[40]	Researcher (nurse)	Phone only	Not stated	Nurse-led follow-up telephone calls based on lifestyle counselling and education. Agreed behavioural objectives were reviewed and barriers were addressed through problem solving. Family participation was encouraged throughout.
Polack *et al*[41]	Pharmacist	In person only	Not stated	Received predischarge pharmacist-led education around the benefits and risks of cardiac medications. Sessions included use of a patient education tool.
Polsook *et al*[42]	Researcher (nurse)	In person and phone	Not stated	Comprised a 4-week self-efficacy enhancement program that targeted patients' motivation to be adherent, skills development and adherence self-monitoring.
Redfern *et al*[43]	Other (physiotherapist)	In person and phone	Not stated	Based around risk factor assessment and goal setting. Patients chose their risk factor module and self-committed to a written action plan. Received a resource pack that included information leaflets. Follow-up sessions tested patients' knowledge of their risk factors. Personal goals were also identified and positive. Risk-lowering behaviour recorded.

Continued

Table 3 Continued

Author	Intervention features			
	Interventionist	Delivery method	Theoretical basis	Intervention summary
Redfern *et al*[44]	Other (physiotherapist)	In person and phone	Not stated	Based around risk factor assessment and goal setting. Patients chose their risk factor module and self-committed to a written action plan. Received a resource pack that included information leaflets. Follow-up sessions tested patients' knowledge of their risk factors. Personal goals were also identified and positive. Risk-lowering behaviour recorded.
Uysal and Ozcan[45]	Researcher (nurse)	In person and phone	Not stated	Individualised education plans around lifestyle and risk factor management. Received access to a computer-based education along with brochures on lifestyle changes post-MI. Telephone counselling during follow-up addressing negative health behaviours, including treatment non-adherence.
Xavier *et al*[46]	Other: community health worker	In person and phone	Not stated	Involved personalised counselling to help overcome barriers to adherence and lifestyle modification. Also received an adherence calendar to record medication taking and were asked to complete diaries, which included information about their medications. Family participation encouraged.
Sharma *et al*[47]	Other: community health worker	In person and phone	Not stated	Involved personalised counselling to help overcome barriers to adherence and lifestyle modification. Also received an adherence calendar to record medication taking and were asked to complete diaries, which included information about their medications. Family participation encouraged.
Yorio *et al*[48]	Nurse or pharmacist	In person only	Not stated	Postdischarge session with nurse or pharmacist. Session included full medication review and titration, risk factor counselling and discussion/referral to cardiac rehab and other HCPs (dietician and/or smoking cessation service).

ACS, acute coronary syndrome; CG, control group; CMAS, Composite Medication Adherence Score; CS-SRM, Common-Sense Model of Self-Regulation; HBS, Health Behaviour Scale; HCP, healthcare provider; IG, intervention group; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac events; MARS, Medication Adherence Report Scale; MDT, multidisciplinary team; MI, myocardial infarction; MMAS-4, Morisky Medication Adherence Scale (4-item); MMAS-8, Morisky Medication Adherence Scale (8-item); MPR, medication possession ratio; MRA, medical regimen adherence; NCF, necessity concerns framework; NR, not reported; PDC, proportion of days covered; PST, problem-solving therapy; RCT, randomised controlled trial; TRA, theory of reasoned action.

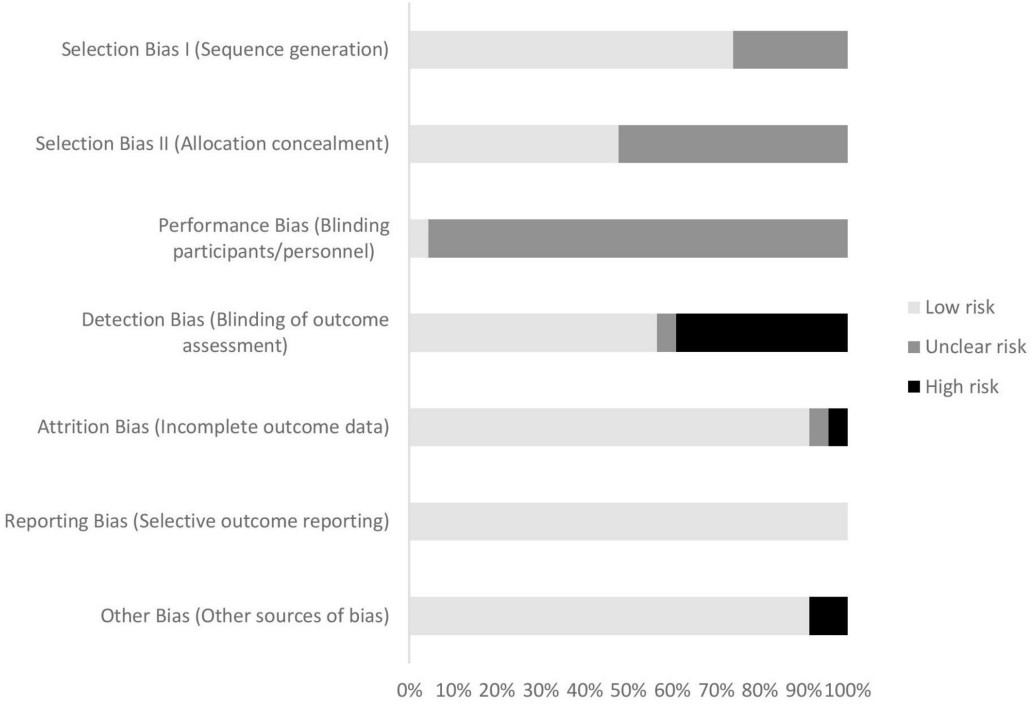

Figure 2 Risk of bias assessment.

included phone contact (k=12, OR 1.63, 95% CI 1.25 to 2.12), and there was a trend for better-quality studies (ie, 'low' risk of bias) to increase the odds of adherence (k=6, OR 1.69, 95% CI 1.15 to 2.47). A negligible positive effect was found for interventions delivered by nurses (k=11, OR 1.19, 95% CI 1.04 to 1.36), and pharmacist-led interventions had a small though non-significant effect on medication adherence (k=6, OR 1.44, 95% CI 0.92 to 2.26). Studies led by HCPs other than nurses and pharmacists (ie, physicians,[25 39] physiotherapists,[44] problem-solving therapists,[34] community health workers[46]) yielded a small positive effect on medication adherence (k=5, OR 1.66, 95% CI 1.22 to 2.24). We found no discernible differences in effect size between studies that included adherence as a primary or secondary outcome, and a small number of theoretically informed studies had a non-significant trend towards a negative effect on adherence (k=4, OR 0.94, 95% CI 0.60 to 1.49).

DISCUSSION

The primary objective of this study was to identify interventions led by HCPs to improve medication adherence following ACS. Meta-analysis revealed a small effect of HCP-led interventions on medication adherence. Our results are consistent with previous meta-analysis studies that have looked at the effectiveness of adherence interventions in other cardiac patient populations.[5 17]

In line with recent adherence literature,[49] the majority of intervention studies identified were delivered by nurses or pharmacists. However, we found no indication that study effectiveness was moderated by the HCP delivering the intervention. Studies that included nurses in their delivery had a negligible effect towards better medication adherence, which does not correspond to findings from another meta-analysis that found that nurse-led interventions had a small to medium effect on adherence in patients with CAD.[5] Six pharmacist-led interventions had a small but non-significant effect on medication adherence, which is congruous with previous reviews across cardiac-related diseases.[5 17] Objectively, pharmacists should be ideal candidates to deliver adherence interventions due to the necessary knowledge and skills they possess to promote and support medication-taking behaviour.[50] A meta-analysis of 771 medication adherence intervention trials found that the most effective interventions were delivered by pharmacists,[49] which suggests that pharmacists may be better utilsied in other patient populations. Our findings should, however, be interpreted with caution due to the small number of pharmacist-led studies included in our analyses.

In terms of delivery method, interventions that included phone contact had higher odds of medication adherence compared with interventions delivered exclusively in person. Phone-delivered interventions may be a more convenient method to reach patients after discharge to monitor and encourage good medication adherence over time. Half of the interventions that included phone contact also contained a face-to-face predischarge component. Cutrona *et al*[51] found that two-thirds of interventions delivered at discharge were effective at improving adherence to cardiovascular medicines. Periods of care transition such as during hospital discharge are ideal opportunities to discuss treatment to pre-empt potential barriers to regimen adherence. Moreover, the dynamic nature of adherence dictates that monitoring of

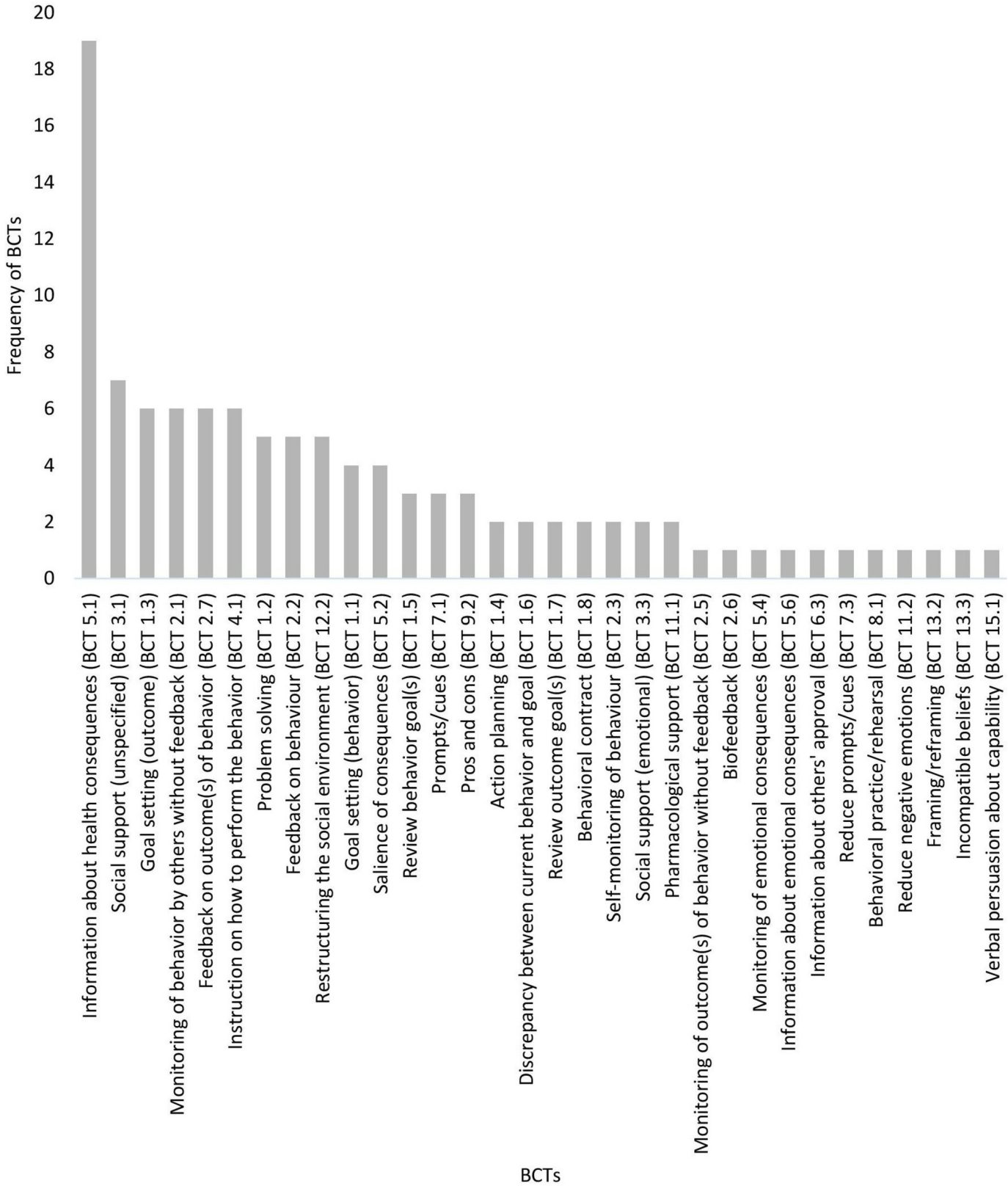

Figure 3 Frequency of BCTs identified among interventions. BCT, behaviour change technique.

medication-taking behaviour over time by both patients and/or HCPs is crucial to ensure therapy maintenance for long-term conditions such as ACS.

We expected to find a greater proportion of interventions that used theoretical approaches to change medication-taking behaviour. There were only four studies that reported a theoretical basis, of which just one was based on a model of medication-taking behaviour (necessity–concerns framework[52]). A review by Conn *et al*[53] found that theory-driven interventions had a

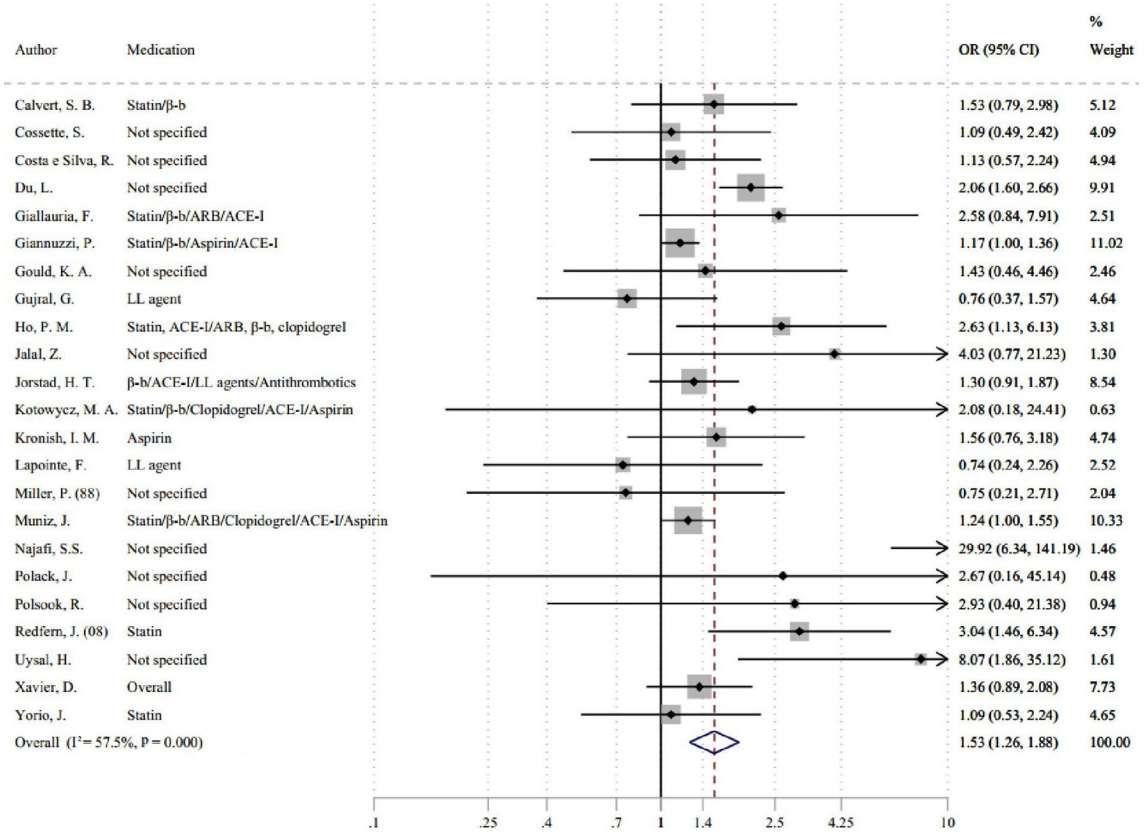

Figure 4 Forest plot showing pooled effects size for healthcare-provider-led interventions on medication adherence (k=23, includes outliers).

significant but modest effect on medication adherence. Our findings suggest that theory-driven adherence interventions for ACS are lacking, thus highlighting an important avenue for future research.

Coding intervention content

To our knowledge, this review is the first to use the BCT taxonomy to code interventions that targeted adherence across all cardiac medications following ACS. The BCT taxonomy provided a useful tool to analyse the content of adherence interventions, and we found that one-third of all BCTs detailed in the taxonomy were identified in at least one intervention. This relatively small number of total BCTs identified was unsurprising as many were not applicable to medication-taking behaviour. It is likely that additional strategies may have been used among interventions but were not identified due to a lack of detail in the description of the intervention. A lack of transparency in study reporting is an issue that limits the usability and replicability of interventional research. Checklists such as TIDieR[54] are becoming commonplace to improve the quality of intervention reporting.

Written, verbal or visual information provision about the consequences of adherence (BCT 5.1) was by far the most frequently used BCT among HCP-led interventions. Discussing the consequences of non-adherence may help to strengthen patients' beliefs in the necessity of their medications, which have been shown to predict non-adherence.[55] While information is necessary to improve patients' knowledge, it is not sufficient as a stand-alone strategy to change behaviour. Information-only strategies have been found to be generally ineffective at changing complex behaviours such as adherence.[56]

Clinical and research implications

Medication taking is a complex behaviour that can be difficult to change. Targeting patients identified with an adherence issue rather than all medication-takers may be one strategy to improve the effectiveness of adherence interventions. Cutrona *et al*[57] reported that 'broad' interventions (target all medication-takers) were less effective than 'focused' (target non-adherers only). None of the studies identified in this review targeted non-adherers; therefore, it is not yet known whether 'focused' interventions would be more appropriate for patients with ACS.

There were a variety of adherence measures used among included interventions, most of which were non-validated self-report tools. While an approach that combines self-reporting with an objective measure (eg, prescription refill records) is considered best practice, just two interventions followed this guidance. No studies used electronic monitors (eg, Medication Event Monitoring System) that provide real-time data on medication-taking behaviour[58] and have been used to good effect in studies with patients with hypertension,[59] heart failure[60] and CAD.[61] There is potential

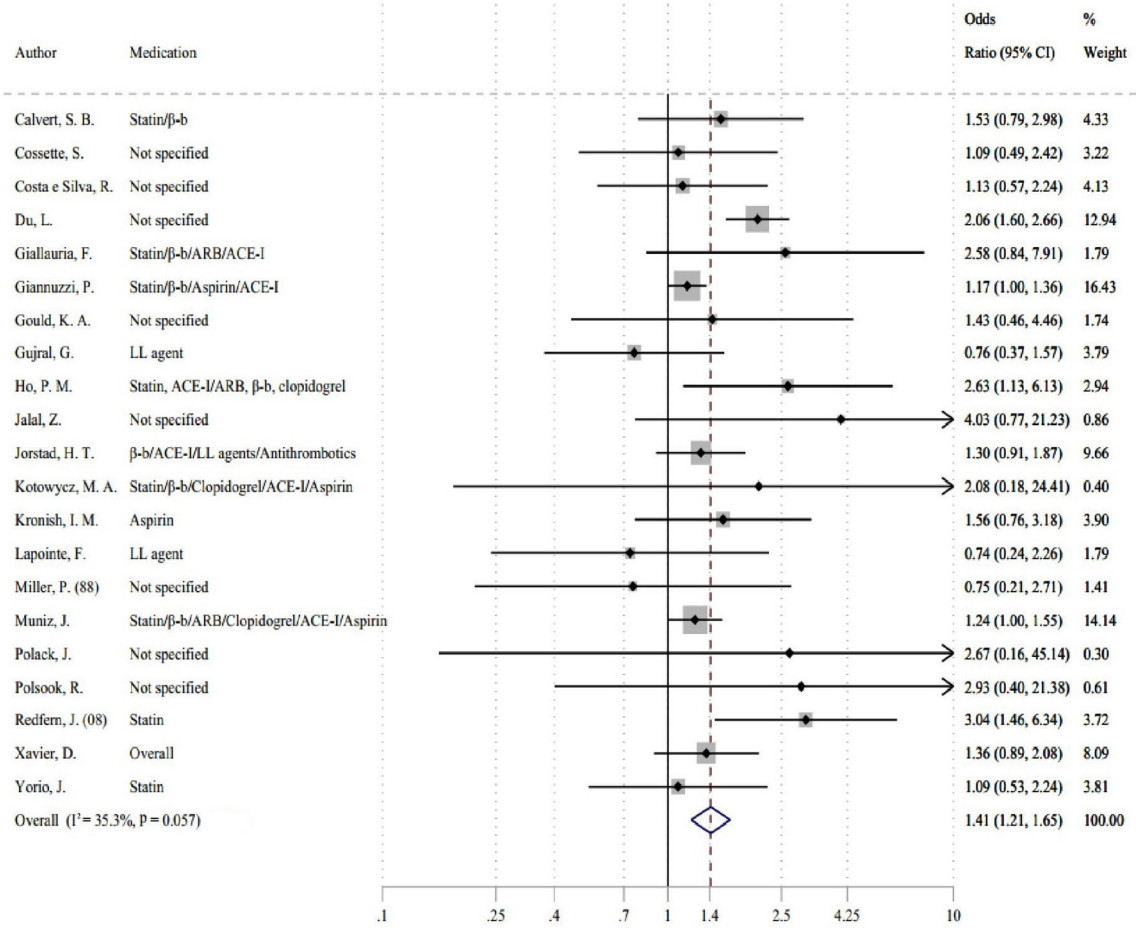

Figure 5 Forest plot showing pooled effects size for healthcare-provider-led interventions on medication adherence (k=21, outliers removed).

for objective measures to be used in conjunction with self-report tools to provide a more reliable and accurate representation of medication-taking behaviour of patients with ACS.

Strengths and limitations

The strengths of this study include the adoption of a comprehensive search strategy that comprised eight online databases and a supplementary grey literature search. Additionally, we applied an existing behaviour change framework to identify specific techniques used among HCP-led adherence interventions, which we believe is a novel approach for trials with patients with ACS. Our study does also include certain limitations. First, while we were successful in BCT identification, there were insufficient data to determine the effectiveness of particular BCTs. A larger data set would be required to undertake the type of meta-regression analyses that have recently been reported within the adherence literature.[62] Second, we found relatively high levels of statistical heterogeneity in our random-effects models, which is inherent when comparing methodologically diverse behavioural interventions. We accounted for this variability by removing outliers, which resulted in our final model having moderate statistical heterogeneity. Third, only one researcher was involved in all aspects of the identification, screening, data extraction and risk of bias assessments, although dual-raters coded interventions independently using the BCT taxonomy. Best practice would be to include multiple independent raters in all stages of the review to ensure methodological rigour. Fourth, we decided not to exclude studies based on how medication adherence was measured, which was often done using unreliable self-report methods. A previous review by Santo *et al*[63] circumvented this issue somewhat by including stricter adherence measurement eligibility criteria. Ultimately, all methods of adherence measurement are limited in terms of practicality, reliability and cost, which represents a wider issue across the adherence literature.

CONCLUSION

This study suggests that HCP-led interventions have a small positive effect on medication adherence following ACS. An existing BCT taxonomy was used successfully to identify common techniques within adherence interventions. However, data were insufficient to draw firm conclusions regarding the impact of BCTs on intervention

Table 4 Overall effects and subgroup analyses for medication adherence interventions

	k	N	OR	CI	I² (%)	P heterogeneity	P bias
Overall							
All studies	23	9735	1.54	1.26 to 1.88	57.5	0.001	0.066
Excluding outliers	21	9545	1.41	1.21 to 1.65	35.3	0.057	0.286
Interventionist							
Pharmacist	6	813	1.44	0.92 to 2.26	30.0	0.210	0.309
No pharmacist	15	8732	1.41	1.19 to 1.68	41.0	0.049	0.439
Nurse	11	5030	1.19	1.04 to 1.36	0	0.920	0.501
No nurse	10	4515	1.63	1.26 to 2.10	52.1	0.027	0.454
Other HCPs	5	3842	1.66	1.22 to 2.24	67.1	0.012	0.550
Nurse or pharmacists	16	5703	1.21	1.07 to 1.38	0	0.663	0.167
Delivery method							
In person only	9	6358	1.21	1.08 to 1.36	0	0.890	0.305
Included phone contact	12	3187	1.63	1.25 to 2.12	32.0	0.135	0.629
Theoretical basis							
Theory based	4	686	0.94	0.60 to 1.49	0	0.781	0.692
Not theory based	17	8859	1.48	1.25 to 1.76	41.4	0.038	0.094
Outcome							
Primary	12	3833	1.31	1.11 to 1.54	0	0.622	0.227
Secondary	9	5712	1.48	1.12 to 1.96	63.1	0.006	0.548
Risk of bias							
Low risk	6	3948	1.69	1.15 to 2.47	51.4	0.068	0.042
Higher risk	15	5597	1.36	1.13 to 1.64	28.1	0.147	0.658

HCP, healthcare provider; I², heterogeneity; k, number of studies; N, sample size; P bias, small study effects significance; P heterogeneity, heterogeneity significance.
Interventionist, delivery method and theoretical basis were prespecified subgroups, while outcome and risk of bias were determined post hoc. Outliers were excluded from subgroup analyses.[40 45]

effectiveness. Information provision remains the basis of most adherence interventions. Further work is required to understand how intervention design and delivery determines the effectiveness of adherence interventions following ACS.

Contributors Concept design was undertaken by JC, VA and JW. JC undertook the literature search with VA and JW involved in eligibility screening. LA and SN contributed to behaviour change technique coding and statistical analyses, respectively. JC wrote the first draft, with all authors contributing to the critical revision of the manuscript.

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