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REVIEW ARTICLE

Interventions promoting adherence to cardiovascular medicines

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Abstract *Background* Cardiovascular diseases (CVDs) are a large burden on the healthcare system. Medicines are the primary treatment for these diseases; however, adherence to therapy is low. To optimise treatment and health outcomes for patients, it is important that adherence to cardiovascular medicines is maintained at an optimal level. Therefore, identifying effective interventions to improve adherence and persistence to cardiovascular therapy is of great significance. *Aim of the Review* This paper presents a review of the literature on interventions used in the community setting which aim to improve adherence to cardiovascular medicines in patients with hypertension, dyslipidaemia, congestive heart failure or ischaemic heart disease. *Methods* Several databases (Medline, EMBASE, PsychINFO, IPA, CINAHL, Pubmed, Cochrane) were searched for studies which were published from 1979–2009, evaluated interventions intended to improve adherence to cardiovascular medicines in the community setting, had at least one measure of adherence, and consisted of an intervention and comparison/control group. *Results* Among 36 eligible studies (consisting of 7 informational, 15 behavioural, 1 social, and 13 combined strategy interventions), 17 (1 informational, 10 behavioural, and 6 combined) reported a significant improvement in adherence and/or persistence. Behavioural interventions were the most successful. Twenty-one studies (4 informational, 9 behavioural, and 8 combined) also demonstrated improvements in clinical outcomes, though, effects were frequently variable, contradictory and not related to changes in adherence. *Conclusion* Several types of interventions are effective in improving adherence and/or persistence within the CVD area and in the community setting. Behavioural interventions have shown the greatest success (compared to other types of interventions); and adding informational strategies has not resulted in further improvements in adherence. Improving adherence and persistence to cardiovascular medicines is a dynamic process that is influenced by many factors, and one which requires long term multiple interventions to promote medicine taking in patients

Keywords Adherence · Cardiovascular diseases · Community healthcare setting · Interventions · Primary care setting

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Impacts on Practice

- The key to the success of pharmacotherapies in achieving therapeutic goals in cardiovascular disease is ongoing patient adherence and persistence to prescribed medicines.
- Interventions developed and reported in the literature to improve adherence to cardiovascular medicines are either informational, behavioural or a combination. Most are anecdotal, with some evidence-based in cardiovascular diseases (CVDs), and a few in other chronic diseases.
- Behavioural interventions are the most effective in improving adherence in the CVD area in the community setting. The motivational counselling and the expert

system based on the Trans-Theoretical Model are also promising interventions.
- Healthcare professionals should consider behavioural interventions as the more effective strategies in supporting patient adherence.

Introduction

Cardiovascular disease (CVD) is a leading cause of death, morbidity and disability in both developed and developing countries and imposes an enormous and escalating clinical, economic and public health burden. Globally, an estimated 17.3 million people died from CVD in 2008, representing 30% of all deaths [1]. In recent decades, a vast array of evidence based pharmacotherapies for both the primary and secondary prevention and management of CVD have become available. Most CVDs are preventable, and therefore primary prevention is important in that it can significantly reduce the number of first cardiac events. However, in patients with established CVD, secondary prevention is essential to reduce recurrent events, improve survival and quality of life. The evidence based pharmacotherapies include anti-anginal medicines, antihypertensives, lipid-lowering medicines, antithrombotic and antiplatelet agents. A key to their success in achieving therapeutic goals, however, is ongoing adherence (defined as the extent to which a person's behaviour in terms of their medication taking, corresponds with agreed recommendations from a healthcare provider [2]) and persistence (defined as the overall duration of treatment—how long patients continue to take their medicines [3]) to prescribed medicines, which applies equally to the management of symptomless medical conditions such as hypertension and dyslipidaemia, as well as noticeable cardiovascular complications such as ischaemic heart disease (IHD) and heart failure. Indeed, clinical trials have shown that being adherent to treatment regimens is in general related to a better prognosis than being non-adherent [4, 5].

Research, however, has shown that patient adherence to cardiovascular medicines is suboptimal, ranging from 11 to 83%, depending on the disease and medicine [3], as well as on the definition of adherence and method of measurement. Hence, non-adherence to medicines represents a significant factor contributing to morbidity, hospital admissions, mortality and health system costs associated with CVD [3, 6–8]. Therefore, improving patient adherence is of great importance in reducing morbidity, hospital admissions, mortality and overall healthcare costs. Extensive research has been conducted to identify and evaluate interventions that aim to improve medicine adherence in patients with CVDs. Many interventions have been developed and evaluated, however, most have produced only modest improvements [3]. Nevertheless, it is important that healthcare professionals are aware of the effective practical interventions or strategies, and are up skilled to deliver them in the community healthcare setting.

This paper presents a review of the literature on interventions used in the community setting which aim to improve adherence to cardiovascular medicines in patients with hypertension, dyslipidaemia, congestive heart failure or IHD. Whilst other reviews have been recently published (e.g. Glynn et al. [9], Schedlbauer et al. [10], Haynes et al. [11]), they have either been focused on improving clinical outcomes only [9], or have only included randomised controlled trials (RCTs) [10, 11]. This review includes several research designs, has a community setting focus, and investigates the impact of non-medication interventions on adherence to therapy as the key outcome in four CVD areas.

Methods

Several databases (Medline, EMBASE, PsychINFO, International Pharmaceutical Abstracts, CINAHL, Pubmed and the Cochrane Library) were searched for articles published between January 1979 and September 2009. The keywords used in the search strategy were "adherence or non-adherence" or "compliance or noncompliance" or "treatment refusal or discontinuation" or "non-persistence or persistence"; and "cardiovascular diseases or hypertension or hyperlipidaemia or dyslipidaemia or chronic heart failure or ischaemic heart disease"; and "intervention studies or intervention or education or behaviour or social support". Articles were restricted to English. The references of the retrieved articles were also searched for relevant articles.

Study selection

Retrieved articles were screened based on their title, index terms and abstract. The full texts of potentially relevant articles were reviewed to determine their relevance and satisfaction of the inclusion criteria. The following research designs were included: randomised and nonrandomised, controlled and uncontrolled, prospective and retrospective, qualitative and quantitative, and observational studies.

Original research articles which met the following inclusion criteria were selected: evaluation of an intervention aimed at promoting adherence to cardiovascular medicines; at least one outcome measure of adherence; in the community setting or in clinics within hospitals that service ambulatory patients; an intervention and comparison/control group; and focusing on CVD, specifically hypertension, dyslipidaemia, chronic heart failure and IHD.

Studies were excluded if they involved hospital inpatients; if adherence was not measured as an outcome; or if one of the goals of the intervention was not to affect adherence to self-administered medicines. Studies were also excluded if the intervention was a change in medicine or dose frequency. There were no restrictions regarding the methods or tools used to measure adherence. However, as a variety of methods were used, some valid and reliable, a direct comparison between the outcomes, for example in terms of odds ratios, was not possible.

Review process

The following data were extracted by one reviewer for each eligible study, and a sample (25%) checked by a second reviewer: study design, characteristics of the study population, description of the actual intervention, description of the comparison/control arms, the outcomes measured and their results. When outcomes were measured at multiple time points, data were extracted from all measurement times to assess the change over time.

As the patient populations and methods of the included studies differed (e.g. the care that comparison groups received and measurement methods), it was inappropriate to pool the results or conduct a meta-analyses of the identified randomised trials. The studies were grouped by intervention type: informational, behavioural, social and combined strategy interventions [12]. Informational interventions were defined as those which aim to educate and motivate patients by means of instructions and education. Education and motivation should lead to better understanding of the disease and medicine by the patient, thereby, indirectly leading to better adherence. The primary goal of behavioural interventions is influencing behaviour. Behaviour can be altered through reminding, rewarding or shaping. Social interventions involve the support of family or friends in changing adherence to medicines. Combined strategy interventions were defined as those that include a mix of the above interventions and featured at least two intervention categories. The complex nature of some interventions made it difficult to categorise the interventions. Interventions were categorised according to their most prominent components.

Additionally, the interventions were further categorised according to the evidence used in developing their structure and content: evidence, theory and anecdotal-based interventions. Evidence-based interventions were defined as those which have been shown in earlier studies to have a positive impact on adherence to cardiovascular or other chronic disease medicines. Theory-based interventions were defined as those which were based on theoretical models e.g. the health belief model. Anecdotal interventions were defined as those which were developed to address the factors which affect adherence, such as lack of social support or knowledge of the disease, but their impact on adherence has not been evaluated.

The studies were also divided by type of prevention: primary or secondary. For the purposes of this review, primary prevention was defined as prevention of the occurrence of a first cardiac event and secondary prevention as the prevention of a second or next cardiac event as reported in the articles.

Results

The electronic search resulted in 9,621 citations, of which 215 appeared to fulfil the inclusion criteria. The full text of each article was reviewed, resulting in a total of 36 eligible articles (Table 1). Eight studies focused on patients with heart failure (Table 1), three on patients with dyslipidaemia, 21 on patients with hypertension, and one each on patients with IHD, dyslipidaemia and IHD, type 2 diabetes and hypertension, and patients on specific cardiovascular medicines. Interestingly, no pattern could be detected in the types of study designs based on the condition. There were 21 RCTs [13–33], seven randomised prospective studies [34–40], two open-label studies [41, 42], two longitudinal studies [43, 44], one cross-over study [45], one pilot study [46], one follow-up study [47], and one study consisting of a prospective observational and a randomised controlled trial phase [48]. Of the 36 included studies, seven described and evaluated informational interventions [14, 15, 19, 24, 28, 34, 36, 39] behavioural interventions [16, 17, 22, 27, 30, 31, 33, 35, 37, 38, 40, 41, 43–45], one a social intervention [10, 13] combined strategy interventions [14, 18, 23, 25, 26, 29, 32, 42, 46–48], and two studies compared an informational intervention with a combined strategy interventio [20, 21].

The majority of interventions were classified as anecdotal (n = 15) [10, 15, 16, 20, 21, 24, 28, 35–38, 41–45, 48] interventions were evidence-based in CVD [14, 18, 19, 23, 25, 29, 33, 34, 41, 46, 47], and three were evidence-based in other chronic diseases [26, 27, 39]. Seven studies evaluated an intervention based on theory [13, 17, 22, 30–32, 40]. Improvements in adherence and/or persistence were reported in seven anecdotal-based [15, 37, 38, 43–45, 48], three evidence based in CVD [18, 23, 47], one evidence-based in other diseases [27], and six theory-based interventions [17, 22, 30–32, 40].

All 36 intervention studies were targeted at patients; however, in ten studies the intervention also targeted healthcare professionals and in one study, volunteer non-healthcare professionals. Pharmacists [14, 15, 17, 25, 26, 46], nurses [13, 18, 34], physicians [14, 25, 42, 46], research assistants [30], and volunteer non-healthcare professionals

Table 1 Characteristics of 36 studies which were included in this review and which evaluated interventions aimed at improving adherence to cardiovascular medicines

Study	Design	Country	Population	Number in Intervention/Control groups (initial recruited)	Threshold for good adherence	Study duration (months)
Murray et al. [15]	RCT	USA	Heart failure	122/192	Administration within 2.4 h of the previous dose (once-daily), or within 1.2 h of the previous dose (twice-daily)	12
Udelson et al. [16]	RCT	USA	Heart failure	136/133 + 136[a]	Not described	5
Bouvy et al. [17]	RCT	The Netherlands	Heart failure	74/78	MEMS was opened ≥ 80% of the days	6
GESICA investigators [18]	RCT	Argentina	Heart failure	760/758	Not described	9
Strömberg et al. [34]	PS	Sweden	Heart failure	82/72	Not described	6
Schmidt et al. [43]	LS	Germany	Heart failure	32/30	Not described	6
Wakefield et al. [19]	RCT	USA	Heart failure	47 + 52/49[b]	Not described	6
Holland et al. [14]	RCT	UK	Heart failure	149/144	Not described	6
Pearce et al. [20]	RCT	USA	Type 2 DM with hypertension	50 + 58/91[b]	Not described	12
Schectman et al. [21]	RCT	USA	Hyperlipidaemia	52/50 + 29/31[c]	Not described	6
Guthrie et al. [35]	PS	USA	Hyperlipidaemia	2765/10335	Not described	6
Faulkner et al. [22]	RCT	USA	Hyperlipidaemia	15/15	≥80% of pills taken	24
Brown et al. [45]	CO	USA	Hyperlipidaemia and ischaemic heart disease	31[d]	Not described	28
Powel and Edgren [36]	PS	USA	Patients on benazepril, metoprolol, simvastatin	1993/2253	≥80% of pills taken	9
Coull et al. [23]	RCT	UK	Ischaemic heart disease	165/154	Not described	12
Patel et al. [44]	LS	USA	Hypertension	795/735 + 1163 + 652 + 1358[a]	≥80% of pills taken	12
Johnson et al. [40]	PS	USA	Hypertension	500/517	Not described	18
Saito and Saruta [24]	RCT	Japan	Hypertension	9871/706	Not described	12
Barrios et al. [41]	OLS	Spain	Hypertension	485/1038	≥80% of pills taken	3
Planas et al. [25]	RCT	USA	Hypertension	32/20	≥80% of pills taken	9
De Castro et al. [26]	RCT	Brazil	Hypertension	34/37	The presence of hydrochlorothiazide	6
Dusing et al. [42]	OLS	Germany	Hypertension	101/105	Daily intake of medicines between 7 am and 11 am	8
Schneider et al. [27]	RCT	USA	Hypertension	47/38	Not described	12
Schroeder et al. [14]	RCT	UK	Hypertension	128/117	Not described	6
Hunt et al. [28]	RCT	USA	Hypertension	302/302	Not described	12
Hunt et al. [29]	RCT	USA	Hypertension	230/233	Not described	12
Friedman et al. [30]	RCT	USA	Hypertension	299, results available for I = 133, C = 134	≥80% of pills taken	6
Márquez-Contreras et al. [37]	PS	Spain	Hypertension	212 + 212/212[b]	80–110% of pills taken	18
Márquez-Contreras et al. [38]	PS	Spain	Hypertension	125/125	80–110% of pills taken	12

Table 1 continued

Study	Design	Country	Population	Number in Intervention/Control groups (initial recruited)	Threshold for good adherence	Study duration (months)
Chabot et al. [46]	Pilot	Canada	Hypertension	111, results available for I = 41, C = 59	≥80% of pills dispensed	9
Thomas and Micelli [39]	PS	USA	Hypertension	174/173	Not described	6
Ogedegbe et al. [31]	RCT	USA	Hypertension	95/95	One pill taken once-daily	12
Sclar et al. [47]	FUS	USA	Hypertension	163/181 + 50/59[e]	Not described	6
Mohammadi et al. [32]	RCT	Iran	Hypertension	75/75	Not described	12
Lee et al. [48]	PS + RCT	USA	Hypertension	PS: 200 RCT: 83/76	≥80% of pills taken	14
Mehos et al. [33]	RCT	USA	Hypertension	18/18	Not described	6

C comparison group, *CO* cross-over study, *DM* diabetes mellitus, *FUS* follow-up study, *I* intervention group, *LS* longitudinal study, *MEMS* medication event monitoring system, *OLS* open-label study, *PS* prospective study, *RCT* randomised controlled trial

[a] This study had multiple comparison groups

[b] This study had multiple intervention groups

[c] This study investigated the influence of the intervention on two different medicines, niacin and bile acid sequestrants respectively

[d] This study consisted of 2 groups both exposed to the intervention at different times during the study, total was 31 patients

[e] This study investigated two different populations, existing and newly diagnosed patients, both with an intervention and comparison group

[23] received diverse training sessions and/or recommendations to enhance their intervention delivery skills (e.g. communication skills, making a diagnosis and measuring outcomes) and optimise the patients' treatment. All studies evaluated the impact of the intervention on the patients, however, only two studies focused on evaluating the impact of training quality of delivery of the intervention by the healthcare professionals as well [14, 31].

Only two studies explicitly identified their intervention as both primary [35] or secondary [23] prevention. However, in 18 studies we classified the interventions based on the information gathered from the study inclusion criteria and subject demographics. Five interventions could be considered as primary prevention [27, 36, 42, 44, 47], and three as secondary prevention [14, 19, 22]. Significant improvements in adherence were seen in four [27, 42, 44, 47] and two [21, 22] of the studies with interventions classified as primary and secondary prevention, respectively. A number of interventions could be considered as primary and secondary prevention as patients with and without a previous cardiac event were included [15–18, 20, 21, 29–31, 41]. However, no comparison was made between patients who did or did not suffer from a cardiac event. In the remaining studies the type of prevention could not be determined due to lack of information.

Measurement of adherence and/or persistence varied widely from self-reports and physician reports to Medication Event Monitoring System (MEMS), pill counts, refill records and even serum drug concentrations. In the majority of studies adherence and/or persistence was measured by self-report [14, 15, 19–21, 23, 24, 28, 29, 31, 32, 34, 35, 39, 40, 43, 46], MEMS [13, 15–17, 31, 38, 41–43], or refill records [15, 21, 25, 27, 33, 36, 44, 47]. A number of studies used two [20–22, 24, 31, 41, 46] or even three [15] measures.

The duration of the studies ranged from 3 to 24 months. On the whole, the longer the duration of the study, the greater its impact on adherence and/or persistence. Twelve of the 16 studies with a duration of more than 12 months (n = 16) reported a significant improvement in adherence and/or persistence. However, only 5 of the 20 studies shorter than 12 months duration improved adherence and/or persistence.

Persistence was measured in 6 studies [18, 21, 24, 42, 44, 48], of which 3 reported a significant improvement as result of the intervention [18, 44, 48]. Adherence was also significantly affected in 2 studies [44, 48].

Informational interventions

The studies that reported an informational intervention (Table 2) were RCT's [15, 19, 24, 28] or prospective studies [34, 36, 39]. The sample sizes ranged from 149 to 4,276 participants. Four of the investigated informational interventions were anecdotal [15, 24, 28, 36], two were

Table 2 Informational interventions evaluated in the reviewed studies

Study	Supporting evidence	Intervention	Target Population	Comparison group	Described measures	Adherence outcome	Other outcomes
Hunt et al. [28]	Anecdotal	Two educational packets, focusing on hypertension, lifestyle modification and compliance	Patients	Usual care: normal care for hypertension	Adherence: self-report Satisfaction with care and prevalence of HBPM: questionnaires[a]	No difference in proportion of patients being adherent	Significant change in hypertension knowledge. No significant changes in mean blood pressure; prevalence of home blood pressure monitoring; satisfaction with care
Murray et al. [15]	Anecdotal	Baseline medication history was taken, verbal instructions were given, written materials were provided, and patients were monitored by a pharmacist	Pharmacists and patients	Usual care: baseline medication history was taken	Adherence: MEMS + self-report + refill records. QOL: chronic heart failure questionnaire. Satisfaction: self-developed questionnaire	After 9 months significant higher % doses taken; % doses taken on time; % of refills. After 12 months no significant higher % doses taken; % doses taken on time; self-reported adherence	Significant improvements in exacerbations requiring emergency department visits or hospitalisation; patient satisfaction No significant changes in QOL improvement after 6 and 12 months
Powel and Edgren [36]	Anecdotal	A videotape program presenting information on the medicine prescribed and the inferred disease state was mailed	Patients	Usual care: no videotapes	Adherence: refill records	No significant higher % adherent patients to benazepril, metoprolol and simvastatin	No other outcomes measured
Saito and Saruta [24]	Anecdotal	Mailed newsletter that emphasized the importance of persistence with medicines and the adoption of lifestyle modifications	Patients	Usual care: no newsletter	Adherence: self-report + physician's impression Reasons for non-persistence: questionnaire[a]	No significant higher % persistence patients (physician's impression). Self-reported persistence was higher. Percentages persistent patients were high in both groups	Main reasons for non-persistence were: reduction of blood pressure (38%), too busy to see a physician (36%), weary of taking. medication (9%)
Strömberg et al. [34]	Evidence based in CVD	Patient education and an interactive multimedia program	Nurses and patients	Patient education	Adherence: self-report Knowledge: self-developed questionnaire QOL: EQ-5D	No significant decrease in change in adherence behaviour	Significant improvement in knowledge after 6 months No significant changes in knowledge after 1 month; QOL after 1 and 6 months
Thomas and Micelli [39]	Evidence based in other diseases	Education through the *Know Your Health* [KYH] program	Patients	Usual care: not described	Adherence: self-report Satisfaction: questionnaire[a]	No significant improvement in adherence after 3 months. No difference in adherence after 6 months	Significant improvements in % of patients at goal after 6 months; DBP after 3 months. No significant changes in % of patients at therapeutic goal after 3 months; SBP after 3 and 6 months; DBP after 6 months; glycosylated haemoglobin level after 3 and 6 months

Table 2 continued

Study	Supporting evidence	Intervention	Target Population	Comparison group	Described measures	Adherence outcome	Other outcomes
Wakefield et al. [19]	Evidence based in CVD	Review of the discharge plan of care with patients during the first intervention contact by telephone or videophone, and reinforced during subsequent contacts	Patients	Usual care: not described	Adherence: self-report Self-efficacy scales: self-efficacy tomanage disease in general and symptoms Satisfaction: patient satisfaction and telehealth specific survey	No significant lower % adherent patients after 3 and 6 months. Percentages adherent patients were high in both groups	No significant changes in readmission rate; mortality; self-efficacy in managing disease and symptoms; satisfaction with care; understanding of medications

CVD cardiovascular diseases, *DBP* diastolic blood pressure, *EQ* EuroQol, *HBPM* home blood pressure monitoring, *MEMS* medication event monitoring system, *SBP* systolic blood pressure, *QOL* quality of life

[a] The used questionnaire is not described in the article

evidence-based in CVD [19, 30], and one was evidence-based in other diseases [39]. This resulted in interventions that varied from simple education by a letter to a complex education program. Interestingly there were no theory-based informational interventions.

Only one study showed a significant improvement in patient adherence after the intervention period [15]. However, this improvement was no longer apparent at follow-up. Improvements, however, were seen in other outcomes. Education resulted in significantly fewer exacerbations of heart failure [15], improvements in patient satisfaction [15], knowledge [28, 30], diastolic blood pressure (DBP) [39], and the proportion of patients who achieved their (prescribed) therapeutic goals [39]. However, Wakefield et al. [19] did not show significant improvements regarding satisfaction, knowledge and blood pressure [19]. In summary, whilst improvements were seen in some outcomes, there were no obvious patterns in the positive impact of informational interventions based on the cardiovascular condition, and no long term impact on adherence.

Behavioural interventions

There was a wide variation in the designs of the studies that evaluated behavioural interventions (Table 3). Interventions were investigated in seven RCT's [16, 17, 22, 27, 30, 31, 33], two longitudinal [43, 44], four prospective [35, 37, 38, 40], one cross-over [45], and one open-label study [41], The sample sizes varied from 29 to 13,100. Seven of the behavioural interventions were anecdotal [16, 35, 37, 38, 43–45], two were evidence-based in CVDs [33, 41], one was evidence-based in other diseases [27], and five were theory-based [17, 22, 30, 31, 40]. Reinforcing adherence by motivational counselling was the most commonly implemented behavioural intervention. Four studies evaluating this type of intervention reported significant changes in adherence behaviour [17, 22, 30, 31]. Other effective intervention included: the use of telephone calls or mailings to encourage patients and remind them of the next visit [37]; adherence packages, which allowed the patient to see if the dose for that day had been taken and what to do if the dose was missed [27]; and changing health related behaviour with a computer generated, individualised expert system based on The Transtheoretical Model (TTM) [40].

Home blood pressure monitoring (HBPM) demonstrated contradictory results. Marquez-Contreras et al. [38] demonstrated improvements in adherence, though Mehos et al. [33] did not report a significant effect. Similarly, with regards to regimen simplification, two studies reported a significant improvement in adherence [44, 45] and persistence [43], while Udelson et al. [16] did not show significant changes.

Table 3 Behavioural interventions evaluated in the reviewed studies

Study	Supporting evidence	Intervention	Target population	Comparison group	Described measures	Adherence outcome	Other outcomes
Barrios et al. [41]	Evidence based in CVD	The use of MEMS	Patients	Usual care: actively monitored pill counts by physician	Adherence: MEMS + pill counts	No significant higher % adherent patients after 1, 2 and 3 months	No significant changes in SBP and DBP after 3 months[c]
Bouvy et al. [17]	Theory based	Motivational counselling	Pharmacists and patients	Usual care: no structured interview or monthly follow-up	Adherence: MEMS Generic QOL: COOP-WONCA Disease specific QOL: MHFQ	Significant fewer days without use	Significant decrease in generic QOL. No significant changes in % of readmitted or death patients; disease specific QOL
Brown et al. [45]	Anecdotal	12 months 4 times/day niacin for all patients. After 12 months cross-over design with polygel controlled-release niacin (2 times/day) vs. 4 times/day niacin	Patients	The same as intervention: cross over	Adherence: pill count TC, LDL, HDL, TRG: blood samples	Significant higher % doses taken	Significant improvements in TC; LDL; HDL; LDL/HDL ratio. No significant changes in TRG
Faulkner et al. [22]	Theory based	Motivational counselling	Patients	Extensive counselling and dietary instructions were given by telephone	Adherence: pill counts + refill records	After 1 and 2 years significant higher % doses taken of lovastatin; % doses taken of colestipol. After 1,5 and 3 months no significant lower % doses taken of lovastatin; % doses taken of colestipol. Percentages doses taken were high in all groups	Significant improvements after 1 and 2 years in TC; LDL; triglycerides. No significant changes in TC after 1,5 and 3 months; LDL after 1,5 and 3 months; triglycerides after 1,5 and 3 months; HDL
Friedman et al. [30]	Theory based	Motivational counselling	Patients	Usual care: regular medical care	Adherence: pill count Blood pressure: sphygmomano-meter Satisfaction: special developed questionnaire	Significant increase in % adherent patients.	Significant decrease in DBP. No significant change in SBP

Table 3 continued

Study	Supporting evidence	Intervention	Target population	Comparison group	Described measures	Adherence outcome	Other outcomes
Guthrie et al. [35]	Anecdotal	Telephone reminders and reminder postcards, to reinforce the messages about coronary risk reduction	Patients	Usual care: including late postal reminders	Adherence: self-report	No significant higher % adherent patients	No other outcomes measured.
Johnson et al. [40]	Theory based	A computer generated, individualised, expert system, based on the Trans-theoretical Model	Patients	Usual care: not described	Adherence: self-report	Significant decrease in non-adherence after 12 and 18 months. No significant decrease in non-adherence after 6 months	Significant improvement in % of patients in action or maintenance after 12 and 18 months No significant changes in % of patients in action or maintenance after 6 months
Márquez et al. [37]	Anecdotal	Mailed message or telephone call reinforcing compliance by means of encouragements and reminding of the visits[d]	Patients	Usual care: routine primary care	Adherence: pill count Blood pressure: sphygmomano-meter	Significant higher % adherent patients after 1, 2, 4 and 6 months in both intervention groups	Significant decrease in SBP (I2 vs. C); DBP (I2 vs. C and I2 vs. I1). No significant changes in SBP (I1 vs. C and I1 vs. I2); DBP (I1 vs. C)
Márquez et al. [38]	Anecdotal	Patients received, apart from a controlled intervention, also an OMRON automatic monitor for HBPM	Patients	Usual care: routine primary care	Adherence: MEMS Blood pressure: sphygmomano-meter	Significant higher % adherent patients; % doses taken; % doses taken on time	Significant decrease in DBP. No significant changes in SBP; % of controlled patients
Mehos et al. [33]	Evidence based in CVD	HBPM	Patients	Usual care: no HBPM	Adherence: refill records Blood pressure: sphygmomano-meter QOL: SF-36	No significant lower % adherent patients	Significant decrease in DBP and mean arterial pressure. No significant changes in SBP; QOL
Ogedegbe et al. [31]	Theory based	Motivational counselling	Research assistants and patients	Usual care: including assessment	Adherence: MEMS + self-report Blood pressure: sphygmomano-meter	Significant increase in % doses taken	No significant changes in SBP; DBP

Table 3 continued

Study	Supporting evidence	Intervention	Target population	Comparison group	Described measures	Adherence outcome	Other outcomes
Patel et al. [44]	Anecdotal	A single-pill therapy combining the antihypertensive medication amlodipine and atorvastatin	Patients	Normal 2-dose regimen[b]	Adherence: refill records	Significant higher % adherent patients after 6 and 12 months vs. all controls; % persistence patients after 6 months vs. all controls	The magnitude of the adherence benefit was smaller when the MPR was used instead the PDC
Schmidt et al. [43]	Anecdotal	Intake reminders. An alarm sounded at the programmed times of intake, and it stopped only when medication was taken out	Patients	Usual care: no medication box	Adherence: MEMS + self-report Health status: SF-12	Significant lower % adherent patients after 6 months (self-report) and doses taken after 2 and 6 months (MEMS)	Significant improvement in mental health in both groups, no comparison between the 2 groups was made
Schneider et al. [27]	Evidence based in other diseases	Daily-dose adherence package	Patients	Usual care: loose tablets	Adherence: refill records	Significant higher % patients who had prescriptions refilled on time; MPR	No significant changes after 6 and 12 months in SBP; DBP
Udelson et al. [16]	Anecdotal	Doses simplification, an open-label once-daily regimen of controlled release carvedilol	Patients	Twice-daily dose of carvedilol[a]	Adherence: MEMS QOL: KCCQ, TSQM and PHQ-8	No significant lower % doses taken vs. C1; higher % doses taken vs. C2. Percentages doses taken were high in all groups	No significant changes in QOL; BNP levels; SBP; DBP; hospitalisations

BNP brain natriuretic peptide, *C* comparison group, *CVD* cardiovascular diseases, *DBP* diastolic blood pressure, *HBPM* home blood pressure monitoring, *HDL* high-density lipoprotein, *I* intervention group, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *LDL* low-density lipoprotein, *MEMS* medication event monitoring system, *MHQF* Minnesota Living With Heart Failure Questionnaire, *MPR* medication possession ratio, *PDC* proportion of days covered, *PHQ* patient health questionnaire, *SBP* systolic blood pressure, *SF* short form, *TC* total cholesterol, *TRG* triglycerides, *TSQM* treatment satisfaction questionnaire, *QOL* quality of life

[a] Usual twice-daily dose of carvedilol IR in a double-blinded fashion (C1) or the analogous once-daily dose of controlled release carvedilol CR in the morning with a placebo substituted for the second daily dose in a double-blinded manner (C2)

[b] In 4 combinations: 1, amlodipine + atorvastatin; 2, amlodipine + other statin; 3, atorvastatin + other calcium channel blocker; 4, other calcium channel blocker + other statin

[c] Results other months not reported

[d] There were 2 intervention groups, 1 received mailed messages (I1) and 1 received telephone calls (I2)

A large number of the interventions improved patients' clinical outcomes. Motivational counselling resulted in reductions in low-density lipoprotein (LDL) [22], total cholesterol [22], triglyceride levels [22], and DBP [22]. Encouragement combined with visit reminders resulted in improved blood pressure levels [37]. Regimen simplification decreased the total cholesterol, high-density lipoprotein (HDL) levels, LDL levels, and the LDL/HDL ratio [45]. Implementation of HBPM resulted in a reduced DBP [33, 38] and mean arterial pressure [33]. Whilst positive results were demonstrated as a result of the behavioural interventions, overall, there were no obvious patterns in the impact based on the cardiovascular condition.

Social interventions

Only one study investigated a social intervention [13]. This theory-based intervention had a sample size of 245 and investigated the effect of nurse support. The aim of the intervention was to provide an opportunity for patients to talk about any problems with their blood pressure lowering medicines. The comparison group received usual care delivered at the general practice they usually go to. The intervention did neither result in significant differences in the percentage of doses taken on time, days with correct dosing, and doses taken, nor any significant changes in systolic and diastolic blood pressure.

Combined strategy interventions

Nine of thirteen studies investigating combined interventions were mainly RCTs (9 of 13) (Table 4). The sample size ranged from 52 to 1,519. Five of the investigated combined interventions were anecdotal [20, 21, 29, 42, 48] six were evidence-based in CVDs [14, 18, 23, 25, 46, 47], one was evidence-based in other diseases [26], and one was theory-based [32]. Most of the combined interventions included informational and behavioural strategies [14, 18, 21, 25, 26, 29, 46–48], three included informational and social components [20, 23, 32], and one combined all three categories [42]. Two of these studies consisted of two intervention groups and compared the combined intervention with an informational intervention [20, 21].

Of the studies with combined informational and behavioural features, only three studies reported significant improvements in adherence [47, 48], and/or persistence [18, 48]. The behavioural components were reinforcing adherence [18], the use of refill reminders [47], and the use of medication aids [48]. Adherence was also significantly improved in two studies with informational and social elements [23, 32]. The social support was given by volunteer lay health mentors [23], or the patients' partners [32]. The intervention with all three categories combined [42], significantly improved adherence during the intervention period. However, the impact faded with time, over the 8 month study duration.

Numerous other outcomes were affected by these interventions. The combination of education and behavioural strategies resulted in fewer hospital admissions [18], better quality of life (QOL) [18], lower blood pressure [25, 29, 46, 48], more patients at their target blood pressure [25, 29], less resource utilisation [29], more frequent home blood pressure recording by the patient [29], and higher physical activity [46]. On the contrary, other studies did not report a change in readmission rate [14], QOL [14], or blood pressure [26]. Combining education and social support positively affected the physical activity [23], dietary habits [23], blood pressure [32], body-mass index [32], HDL level [32], anxiety [32], and QOL [32] of patients. However, Pearce et al. [20] did not report an improvement in blood pressure or QOL. The use of informational, behavioural as well as social elements in a combined intervention, did not improve blood pressure significantly [42]. In summary, there were no obvious patterns in the positive impact of the interventions based on the cardiovascular condition.

Discussion

This review of the literature identified 36 studies which described interventions aimed at improving adherence to cardiovascular medicines in patients with hypertension, dyslipidaemia, congestive heart failure or IHD in the community setting. Approximately half of the studies (n = 17) demonstrated a significant improvement in adherence and/or persistence. In two of the studies [15, 42], the improvements in adherence dropped during the follow-up period. As most of the studies, which had a positive impact on adherence/persistence, lasted longer than 12 months, this suggests that there may be positive correlation between the degree of impact and the duration of intervention. The results also suggest that a form of ongoing intervention may be needed to achieve sustained impact on adherence/persistence.

Twenty-one studies also demonstrated improvements in clinical outcomes. However, there was no consistency in the results. Notably, the effect sizes differed substantially and in some cases were contradictory with respect to a similar type of intervention. Moreover, several studies reported improvements in adherence and/or persistence with no corresponding improvements in clinical outcomes and vice versa.

Overall, no difference was observed in the impact of the interventions when isolating cardiovascular disease into the four conditions of heart failure, hypertension, dyslipidaemia and IHD reviewed. It appeared that the positive impact of

Table 4 Combined interventions evaluated in the reviewed studies

Study	Supporting evidence	Intervention	Target Population	Comparison group	Described measures	Adherence outcome	Other outcomes
Chabot et al. [46]	Evidence based in CVD	Pharmacist intervention program according to the PRECEDE–PROCEED model.	Pharmacists, physicians and patients	Usual care: not described	Adherence: refill records + self-report	No significant higher % adherent patients with a low or high income	Significant decrease in SBP (high income); more physical activity (high income). No significant changes in SBP (low income); more physical activity (low income); health concerns (low and high income).
Coull et al. [23]	Evidence based in CVD	Participation in a mentor-led group.	Volunteer non-HCP workers and patients	Usual care: Receive standard care	Adherence: self-report Physical activity: questionnaire Diet: questionnaire Health status: SF-36	Significant improvement in adherence after 12 months.	Significant improvements in exercise activity, carbohydrate intake, fat intake; saturated fat intake. No significant changes in total events; protein intake; health status
De Castro et al. [26]	Evidence based in other diseases	Pharmaceutical care program by the Dader method	Pharmacists and patients	Sham intervention with a series of cognitive tests	Adherence: plasma levels of hydrochloro-thiazide	No significant lower % patients with hydrochlorothiazide detection.	No significant changes in SBP; DBP; % of indentified drug related problems
Dusing et al. [42]	Anecdotal	Supportive measures for the physicians and patients	Physicians and patients	Usual care: no supportive measures	Adherence: MEMS	Significant higher % of adherent patients after intervention. No significant higher % of adherent patients during follow-up; % of persistence patients. Persistence percentages were high in both groups	No significant change in blood pressure; % patients with blood pressure normalisation
GESICA investigators [18]	Evidence based in CVD	Education booklet + telephone follow up about adherence to diet, adherence to medicines, monitoring of symptoms, control of signs of hydrosaline retention, and daily physical activity	Nurses and patients	Usual care: Followed by their attending cardiologist	Adherence: not described QOL: Minnesota living with heart failure questionnaire	Significant lower % of patients stopped taking drugs	Significant decreases in heart failure admission; all cause hospital admission; cardiovascular admission. Significant better QOL. No significant changes in all cause mortality

Table 4 continued

Study	Supporting evidence	Intervention	Target Population	Comparison group	Described measures	Adherence outcome	Other outcomes
Holland et al. [14]	Evidence based in CVD	Pharmacists educated and encouraged the patients, removed discontinued medicines, provided recommendations to the physician, and reported the need for adherence aids to the local pharmacist	Pharmacists, physicians and patients	Usual care: Not described	Adherence: self-report QOL: EQ-5D	No significant improvements in adherence after 3 and 6 months	No significant changes in number of readmissions; mortality; QOL
Hunt et al. [29]	Anecdotal	Co-located physician-pharmacist team based care on blood pressure control	Patients	Usual care: continue of normal medical care	Adherence: self-report Blood pressure: sphygmomano-meter QOL: SF-36	No significant increase in % adherent patients.	Significant lower SBP; lower DBP; higher % at target blood pressure; higher % patients recording their blood pressure at home; less resource utilisation. No significant changes in QOL; satisfaction; knowledge
Lee et al. [48]	Anecdotal	Comprehensive pharmacy care program including education, the use of adherence aids and regular follow-up	Patients	Phase 1: patients also received the program. Phase 2: the program stopped	Adherence: pill count Blood pressure: sphygmomano-meter	Phase 1: significant increase in % adherent patients (versus baseline value of all patients). Phase 2: significant increase in % adherent and persistence patients (versus comparison group).	Phase 1: A significant decrease in SBP and LDL-cholesterol. No significant change in DBP. Phase 2: A significant decrease in SBP. No significant changes in DBP; LDL-cholesterol
Mohammadi et al. [32]	Theory based	Educational partnership meeting and follow-up meetings	Patients	Usual care: routine and usual methods	Adherence: self-report Blood pressure: sphygmomano-meter QOL: SF-36 Anxiety: Esphil Burger	Significant improvement in adherence.	Significant decrease in average SBP; average DBP; BMI; anxiety score Significant increase in proportion controlled; HDL; QOL score No significant changes in LDL; cholesterol: TRG

Table 4 continued

Study	Supporting evidence	Intervention	Target Population	Comparison group	Described measures	Adherence outcome	Other outcomes
Pearce et al. [20]	Anecdotal	One patient/social person education session followed by 4 quarterly "newsletters."	Patients	30-min patient education session and the 4 patient newsletters.	Adherence: refill records (short term) + self-report (long term) QOL: SF-36 HbA1C + LDL: blood samples	No significant higher % of adherent patients	No significant changes after 6 and 9 months in SBP; HbA1C; physical composite score; mental composite score; LDL
Planas et al. [25]	Evidence based in CVD	MTM services for hypertension and diabetes management once a month	Pharmacists, physicians and patients	Usual care: Information about blood pressure goals	Adherence: refill records	No significant higher % of refills	Significant decrease in SBP after 9 months. Significant increase in participants at goal blood pressure
Schectman et al. [21]	Anecdotal	Telephone contacts to encourage drug continuation and verbal education	Patients	Usual care: routine care of lipid clinic, including oral and written information	Adherence: refill records + self-reports	No significant higher % doses taken of cholestyramine after 2 and 6 months; niacin after 2 months. No significant lower % doses taken of niacin after 6 months. No significant changes in discontinuance rate	No other outcomes measured
Sclar et al. [47]	Evidence based in CVD	Education + refill reminders by telephone and mail.	Patients	Usual care: not described	Adherence: refill records	Significant higher MPR in existing and new cases	No other outcomes measured

BMI body mass index, *CVD* cardiovascular diseases, *DBP* diastolic blood pressure, *EQ* EuroQol, *HbA1C* haemoglobin A1C, *HCP* health care professional, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MEMS* medication event monitoring system, *MPR* medication possession ratio, *MTM* medication therapy management, *SBP* systolic blood pressure, *SF* short form, *TRG* triglyceriden, *QOL* quality of life

the interventions was influenced by the components of the intervention rather than other factors.

The most effective interventions were behavioural interventions. Motivational counselling and computer generated expert systems were very successful in improving adherence. These methods are directed, patient-centred and individualised, which are appropriate approaches to improve adherence as every patient is different. Adherence packages made it simple for patients to see if the dose for a particular day had already been taken and thereby helped patients with one of the factors related to non-adherence, forgetfulness. Telephone calls and mailings aimed at encouraging patients, adherent or non-adherent, and were not judgemental. Interestingly the adding of information/patient education to a behavioural intervention did not result in better outcomes. This implies that adherence may be more related to the patient's self-efficacy and self management skills rather than their knowledge. These findings are consistent with other literature that also found behavioural interventions to be most effective in influencing adherence/persistence to medicine taking, in general, in the context of chronic diseases [12].

No conclusions can be made regarding primary or secondary prevention as in most of the articles it was unclear what kind of prevention it was. Where the level of prevention was reported, both primary and secondary prevention resulted in significant and non-significant improvements in adherence to cardiovascular medicines. Additionally, no firm conclusions can be made about the evidence used in developing the structure and content of the interventions: evidence, theory and anecdotal-based. There are no obvious patterns as to whether the type of evidence has any effect on the impact of the intervention on patient adherence. However, motivational counselling, which is theory-based, appears to be the most effective behavioural intervention in improving adherence.

There are some limitations in the literature reviewed that must be taken into account when evaluating the impact of interventions reported in the selected studies. Firstly, patients were highly selected in some studies, thereby limiting generalisability and external validity. Secondly, not all studies randomised their patients, and this resulted in differences in subjects' baseline characteristics. Thirdly, not all studies reported a power calculation. As estimation of the expected effect size and baseline levels can be difficult, it is possible that study populations were too small, and lack of effect is the result. Fourthly, the baseline levels regarding patients' adherence differed considerably between studies. The absence of a significant change in adherence in studies with high baseline adherence can be the result of the ceiling effect. Fifthly, due to the absence of an ideal method to measure adherence, a wide variety of measurement methods and definitions of adherence were utilised in the studies. Self-reports, MEMS and refill records were the most commonly used measurement methods. These three methods provided similar estimates of adherence when investigating adherence among patients with heart failure or hypertension [49]. However, other studies reported variable correlations between self-report and objective measures, raising the question whether the use of self-reports is the best method of measuring adherence [50, 51]. Additionally, self-reports can be subjective and skew data. Moreover, the use of MEMS itself can be seen as an intervention and may therefore affect outcomes. Sixthly, the various adherence definitions significantly affect interpretation of effects. Some studies included a time interval in which the medicines had to be taken, others only set a minimum number of pills to be taken, some set minimum and maximum limits, while others did not provide a clear definition of adherence. In addition, improvements in adherence were reported in different ways. For example, results reported as percentage of doses taken cannot be compared with results reported as the percentage of adherent patients. This can lead to under- or overestimation of improvements in adherence.

Finally, in 13 studies the intervention was directed at both patients and healthcare professionals. However, only two studies evaluated the performance of healthcare professionals in delivering the interventions. Therefore the impact of the interventions on patients could vary as a result of the effectiveness with which healthcare professionals delivered the interventions, which may have influenced the results. It is imperative that intervention studies also measure process outcomes and evaluate how well healthcare professionals deliver interventions to the patients. This will ensure that the impact of the intervention is not influenced by the deliverer, but rather by the intervention itself.

There are limitations inherent to the methods used. For example, it is possible that studies meeting the inclusion criteria would have been missed if not found in the databases searched or were in languages other than English. Additionally, intervention studies that measured adherence as an outcome measure but the interventions did not focus on improving adherence, would not have been selected and reviewed. Additional research is needed to examine the cost-effectiveness and sustainability of the interventions which resulted in significant improvements in adherence and/or persistence, only 2 studies examined the costs of the programs and only 4 studies followed-up the patients after the intervention period was over. Of the four studies which examined sustainability, two showed that the improvements in adherence lessened with time.

Conclusions

In summary, we found that behavioural interventions are the most effective in improving adherence in the CVD area

in the community setting. The motivational counselling and the expert system based on the TTM are also promising interventions. These findings highlight the importance of motivational counselling as part of consultations between healthcare professionals and patients in order to promote adherence to therapy. Furthermore, healthcare professionals should consider behavioural interventions as the more effective strategies in supporting patient adherence.

However, there are too many limitations in the studies reported to allow a detailed comparison between the components of the different interventions. Our findings suggest the need for future studies to assess theory-based interventions, evaluate interventions with a longer time span which assess sustainability of impact, investigate the delivery of interventions by healthcare professionals (as well as the impact on patients' adherence), and evaluate the cost-effectiveness of potential effective interventions.

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