Interventions to improve adherence to cardiovascular disease guidelines: a systematic review

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Abstract

Background: Successful management of cardiovascular disease (CVD) is impaired by poor adherence to clinical practice guidelines. The objective of our review was to synthesize evidence about the effectiveness of interventions that target healthcare providers to improve adherence to CVD guidelines and patient outcomes.

Methods: We searched PubMed, EMBASE, Cochrane Library, PsycINFO, Web of Science and CINAHL databases from inception to June 2014, using search terms related to adherence and clinical practice guidelines. Studies were limited to randomized controlled trials testing an intervention to improve adherence to guidelines that measured both a patient and adherence outcome. Descriptive summary tables were created from data extractions. Meta-analyses were conducted on clinically homogeneous comparisons, and sensitivity analyses and subgroup analyses were carried out where possible. GRADE summary of findings tables were created for each comparison and outcome.

Results and Discussion: We included 38 RCTs in our review. Interventions included guideline dissemination, education, audit and feedback, and academic detailing. Meta-analyses were conducted for several outcomes by intervention type. Many comparisons favoured the intervention, though only the adherence outcome for the education intervention showed statistically significant improvement compared to usual care (standardized mean difference = 0.58 [95% confidence interval 0.35 to 0.8]).

Conclusions: Many interventions show promise to improve practitioner adherence to CVD guidelines. The quality of evidence and number of trials limited our ability to draw conclusions.

Keywords: Clinical practice guidelines, Cardiovascular disease, Adherence, Systematic review

Background

Cardiovascular disease (CVD) is a leading cause of death in Canada [1]. Successful management of CVD involves not only the treatment of a specific disease, but also treating and preventing risk factors for CVD, including diabetes, dyslipidemia and hypertension [1–3]. However, the management of CVD is complicated by the large number of clinical practice guidelines available for conditions that contribute to this disease. An article by Ray et al. noted there are also discrepancies in recommendations across guidelines, potentially contributing to low adherence rates [2, 4, 5]. A harmonized guideline by Tobe et al. (2011) found there are over 400 recommendations for managing risk factors for heart disease [3].

Given the complexity of the management of this illness, it is imperative that practitioners use guidelines, and the most appropriate guidelines, in caring for patients with CVD and risk factors for CVD. The impact of guideline implementation has been illustrated previously; a review by Grimshaw and Russell found that using guidelines improved clinical practice [6]. Despite evidence to support the use of guidelines, there remains a gap in their implementation [7].

The dissemination of guidelines alone has little to no effect on practice [8], thus many studies have investigated interventions of varying intensity to increase the
uptake of clinical practice guidelines. Numerous studies of interventions to improve the uptake of guidelines in CVD prevention are available. However, their overall impact on guideline adherence and clinical outcomes is unclear. Unverzagt et al. [9] published a systematic review on a similar topic that focused on primary care physicians’ adherence to guidelines, wherein they demonstrated these interventions can have an impact on adherence outcomes. It is important to determine the effect of these interventions on other healthcare providers, as well as determine the impact of these interventions on clinical outcomes, which is yet to be addressed in the literature to our knowledge.

We identified and synthesized the available research evidence about the effectiveness of interventions that target healthcare providers to improve adherence to CVD prevention and treatment guidelines and clinical outcomes. Our secondary objective was to explore characteristics of guideline implementation interventions and contexts that are associated with increased effectiveness. This leads to our research question: what is the most effective intervention to improve the implementation of, uptake of, or adherence to cardiovascular disease-related clinical practice guidelines by healthcare providers in randomized controlled trials?

Methods
As this research did not involve the collection of primary data, we did not seek ethics approval. This review has been registered with PROSPERO 2014:CRD42014010111. Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014010111

Search
A systematic search was conducted using search terms related to “adherence” and “clinical practice guidelines”, which was refined with the help of a medical librarian. We searched the following databases: PubMed, EMBASE, Cochrane Library (including CENTRAL, DARE and HTAs), PsycINFO, Web of Science and CINAHL (all available years, up to June 2014). Grey literature was also searched, including clinicaltrials.gov to identify potential new studies, ICTRP registry database, and ProQuest thesis database. Our search strategy did not impose any limits on language of publication (Additional file 1).

Inclusion criteria
Study design
The included studies were limited to randomized controlled trials (RCTs). We included all types of RCTs, including cluster RCTs, and nested designs.

Population
Studies that enrolled any registered healthcare providers were included. Subgroups of interest for our analyses included comparing physician participants to other healthcare providers (non-physicians). We excluded trials if less than 75% of the participants included were certified, regulated healthcare providers.

Intervention
All studies that evaluated the impact of an intervention on the implementation of, uptake of, or adherence to a clinical practice guideline by a health care provider were included. The guideline of concern had to relate to the prevention or management of CVD, including risk factor management for any of: diabetes, dyslipidemia or hypertension. Guideline definitions were based on authors stating a guideline to be such. A study was deemed to be about the implementation or adherence to a guideline if the trial report explicitly stated that improving use of a clinical practice guideline was the focus of the intervention. Types of interventions included: academic detailing, audit and feedback, educational sessions, continuing medical education (CME) sessions, and ‘other’ (such as reminders or decision support systems).

Comparison group
We selected studies that included at least one control group. Comparison groups included usual care, a similar guideline implementation intervention of differing intensity or duration than the main intervention group, or no intervention (receipt of the intervention at a different time than the intervention group, such as after data collection).

Primary outcomes
We included trials that reported both a measure of guideline adherence and at least one clinical outcome. Measures of adherence included self-reported adherence, prescription review, and chart review. We included studies reporting any relevant clinical outcomes and considered the following groups of outcomes for analyses: mortality, hospitalizations, quality of life, and disease targets. Outcomes assessed at similar time points were combined in our analysis as short term (3–6 months), and long term (7 months or longer).

Study selection and data extraction
Articles were screened based on title and abstract using the inclusion criteria, then based on full text by two independent reviewers. Discrepancies were resolved by consensus.

Data from included articles was extracted in duplicate by independent extractors. We extracted study characteristics (study design, setting and population), a description
of the intervention (the type of intervention, providers, and resources involved), comparison intervention, risk of bias, outcome measurement and results, and funding for the study. Risk of bias was assessed using the Cochrane Risk of Bias tool for RCTs [10]. All discrepancies between extractors were resolved through consensus. Data was managed using spreadsheets created for each extractor. Authors were contacted after data extraction and consensus meetings were completed to request missing data and to check the accuracy of our extractions.

Data analysis
We conducted descriptive analyses of included studies. We conducted meta-analyses (MA) for outcome results when there was sufficient clinical homogeneity across the studies. Clinical homogeneity was based on similar study characteristics (intervention type, outcome and follow-up point of interest). Meta-analyses were conducted in Review Manager (RevMan 5), using a random effects model and forest plots were generated. Intraclass correlation coefficient (ICC) for cluster RCTs were used in our meta-analyses to calculate the effective sample size to ensure the effect of clustering was taken into account in our analyses, as per the Cochrane Handbook [11]. A Z-test was used to assess statistical significance of meta-analysis results and a \( p < 0.05 \) was considered significant.

The adherence and patient outcomes were measured as both dichotomous and continuous outcome measures. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for use in the MA for dichotomous outcomes. Standardized mean differences (SMD) were used for continuous outcomes, as outcomes measuring the same construct were measured on different scales. Most continuous outcome analyses looked at the differences in mean change of each group from baseline, and this value was used in the MA, though some trials reported follow up results in each group, wherein we calculated the change score for each group to use in our MA. In order to impute the standard deviation for the change score in this instance, the standard deviation of the change score from another similar study was used.

We conducted sensitivity analyses to determine the robustness of our results, comparing the results of our analyses including and excluding studies with imputed standard deviations, and excluding studies with high risk of bias (greater than 3 domains rated as high risk of bias). We conducted subgroup analyses considering participant subgroups (physician participants and other healthcare providers), and considering the condition that was the focus of the guideline in the study (acute and chronic CVD conditions or risk factors). We planned to create funnel plots to investigate potential publication bias if at least ten studies were included for a given outcome, however this was not possible. We present a summary of the overall strength of evidence available using GRADE Summary of Findings tables produced using GRADEpro.

Results
Results of the search
We identified 12,255 potentially relevant unique citations. We excluded 12,033 citations during the initial abstract and title screening. We reviewed 222 full text publications and included 38 studies in the review [12–54] (Fig. 1).

Included studies (Table 1)
Eighteen studies took place in the USA, 14 were completed in Europe (the Netherlands, Italy, England, and Norway), two took place in Canada, one in South Africa, one in Brazil, one in Asia-Pacific area, and one in the Virgin Islands. Thirty-five studies included an intervention to improve physician use of guidelines and ten of those studies included a nurse as a target for the intervention; two studies focused on nurses alone, and one study focused on pharmacists. The most common intervention type was educational focused intervention (18/38), followed by audit and feedback (9/38), academic detailing focused interventions (4/38), comprehensive interventions that included education, audit and feedback and an academic detailing component (2/38), and “other” interventions that did not fall into any pre-designated category (8/38). Seven trials included more than one intervention group. All studies included an adherence outcome, as per our inclusion criterion. Disease target was the most common clinical outcome reported (33/38 trials), followed by mortality (11/38). Hospitalization and quality of life data were also reported in 8/38 and 6/38 trials, respectively.

Risk of bias in included studies
Risk of bias summary graphs and tables were created using RevMan (Figs. 2 and 3). Risk of bias was often assessed as unclear due to poor reporting of a methodological procedure. The majority of trials (33/38) were cluster RCTs, therefore additional risk of bias criteria were included for these studies. Random sequence generation was most often assessed to be low risk of bias, while blinding of participants was most commonly rated as high risk of bias.

Effects of interventions
Education intervention
Seventeen trials tested an education-focused intervention and were included in a meta-analysis. These trials overall favoured the intervention, and one meta-analysis was statistically significant. Seven trials (2545 subjects) reported mortality outcomes, three of which reported mortality at a short term time point with an overall odds
ratio of 0.54 (95% CI 0.2 to 1.42). Four trials reported morality at a long term time point with an overall odds ratio of 0.48 (95% CI 0.11 to 1.98). Four trials (979 subjects) reported hospitalizations as an outcome at a long term time point. The overall odds ratio for this outcome was 0.88 (95% CI 0.54 to 1.41). Six trials (2145 subjects) reported disease target results at a short term time point (SMD = −0.32 (95% CI −0.71 to 0.07)) and five trials (2732 subjects) reported this outcome at a long term time point (SMD = −0.09 (95% CI −0.24 to 0.07)) (Fig. 5). Seventeen trials reported adherence outcome data, six (2306 subjects) reported dichotomous data at a short term time point (OR = 2.11 (95% CI 0.90 to 4.97)), four trials (322 subjects) reported continuous data at a short term time point (Fig. 4) and eight trials (6019 subjects) reported dichotomous data at a long term time point (OR = 1.05 (95% CI 0.82 to 1.34)) (Fig. 6).

Audit and feedback
Nine trials included an intervention that focused on audit and feedback, and seven of those trials reported data sufficient to be included in meta-analyses. Three trials (2240 subjects) reported disease target results at a long term time point with an overall effect of −0.44 SMD (95% CI −1.05 to 0.17) (Fig. 5). Six trials (2983 subjects) reported adherence data at a long term time point with an overall odds ratio of 1.39 (95% CI 0.88 to 2.21) (Fig. 6).

Academic detailing
Four trials (6017 subjects) included academic detailing as the focus of the intervention and all of these trials reported data that was included in a meta-analysis for adherence outcome. The overall odds ratio for this comparison was 1.32 (95% CI 0.88 to 1.96) (Fig. 6).

Other interventions
Eight trials included an intervention whose focus did not fit these previous groups. Four trials (1782 subjects) included a decision support tool as the focus of their intervention. The overall odds ratio for this comparison was 1.19 (95% CI 0.83 to 1.70) (Fig. 6).

Sensitivity and subgroup analyses
Sensitivity analysis investigating the impact of imputed standard deviations in continuous data was possible in the education intervention outcome for the disease target outcome at a short term time point. The pooled SMD from six studies in this comparison was −0.32 (95% CI −0.71 to 0.07), while the estimate from the sensitivity analysis, with studies that included imputed standard deviation removed, was −0.27 (95% CI −0.71 to 0.17). Another sensitivity analysis, investigating the impact of high
| Study ID | Topic of trial | Study Design | Population description | Setting | Intervention Description; Intervention 2 description (if applicable) | Type | Duration of treatment period | Comparison intervention | Outcomes measured | Risk of bias rating |
|----------|----------------|--------------|------------------------|---------|------------------------------------------------------------------|------|-----------------------------|------------------------|-------------------|-------------------|
| Ansari, 2003 | Use of beta-blockers in congestive heart failure | cRCT | Specialist doctors and nurse practitioners, patients with CHF | USA, urban medical centre | Nurse facilitator plus healthcare provider educational sessions; provider and patient reminder letters | Other type: Nurse facilitator; notifications | 1 year | Educational sessions, no nurse facilitator | Mortality, hospitalization, adherence (prescription review, chart review) | High risk of bias |
| Baker, 2003 | Guidelines in prioritised review criteria | cRCT | Family doctors, patients with angina | England, general practices | Review criteria; criteria plus feedback | Other type: review criteria | 12 months | Guideline dissemination alone | Disease target (cholesterol), adherence (prescription review, chart review) | Low risk of bias |
| Bertoni, 2009 | Physician adherence to ATP III guidelines | cRCT | Family doctors | USA, primary care practices | CDSS, educational sessions, academic detailing, CME sessions | Education + audit and feedback + academic detailing + CME session | 2 years | educational sessions, CME sessions, guideline mailed to participants | Disease target (cholesterol), adherence (prescription review, chart review) | High risk of bias |
| Bervanger, 2012 | Multifaceted quality improvement intervention in ACS patients | cRCT | Patients with ACS at general public hospitals | Brazil, public hospitals | Training, reminders, checklists, case management, educational sessions | Education | 8 months | Routine care | Mortality, major adverse cardiac events, adherence (prescription review) | Low risk of bias |
| Bonds, 2009 | Compliance to JNC 7 guidelines to improve blood pressure | cRCT | Family doctors | USA, primary care practices | Educational sessions, dissemination of guidelines, academic detailing for physicians, feedback on blood pressure control | Education + audit and feedback + academic detailing + CME session | 2 years | Similar to intervention but focused on ATP III guidelines | Disease target (BP), adherence (prescription review, chart review) | Low risk of bias |
| Browner, 1994 | CME and follow up to improve detection and treatment of high cholesterol | cRCT | Family and internal medicine doctors | USA, general practices | CME seminar; Intensive CME (office visits and educational materials) | Education + CME sessions | 18 months | Educational sessions | Disease target (cholesterol), adherence (chart review) | High risk of bias |
| Carter, 2009 | Physician and pharmacist collaborative model to improve blood pressure | cRCT | Family doctors, patients with hypertension | USA, community based family medicine | Collaborative model, team building exercises, training sessions, educational sessions | Education + other (collaborative model) | 6 months | Collaborative model | Disease target (BP), guideline adherence tool | High risk of bias |
| De Lusignan, 2013 | Audit based education to reduce blood pressure | cRCT | Mixed health care professionals | United Kingdom, primary care | Audit based education consisting of workshops; academic detailing plus workshops | Education + audit and feedback; academic detailing | 2 years | Usual care | Mortality, major adverse cardiac events, adherence target (BP), adherence (prescription review) | Low risk of bias |
| Deales, 2014 | Team based approach to disease and care management | cRCT | Mixed health care professionals | Italy, primary care groups | Recommendations as textbooks and decision algorithms, education sessions | Education | 12 months | Usual care | Disease target (HbA1c), adherence (chart review) | High risk of bias |
| Study | Intervention Description | Study design | Setting | Intervention Details | Duration | Outcomes | Risk of Bias |
|-------|--------------------------|--------------|---------|----------------------|----------|----------|--------------|
| Dijkstra, 2006 | Implementation strategies for diabetes guidelines | cRCT | The Netherlands, hospitals | Educational meetings, feedback, reminder card, diabetes passport, education | Education + audit and feedback | Disease target (HbA1c), adherence (chart review) | High risk of bias |
| Eaton, 2011 | Multimodal intervention to improve screening and management of hyperlipidemic patients | cRCT | Family doctors | PDA with decision support and education toolkit and academic detailing | Academic detailing | Disease target (cholesterol), adherence (chart review) | Low risk of bias |
| Eccles, 2002 | Computerised decision support system to implement angina guidelines | cRCT | England, general practices | Computer decision support that provided access to guidelines | Other: CDSS | Quality of life, adherence (chart review) | Low risk of bias |
| Feldman, 2009 | Simplified algorithm for treatment of hypertension | cRCT | Family practices, patients with hypertension | Algorithm, aids, one follow up meeting, educational materials and sessions | Education + Other (algorithms) | Educational sessions and guidelines | Low risk of bias |
| Fihn, 2011 | Collaborative care model based intervention to improve angina management | cRCT | USA, academic primary care clinics | Expert advice, progress evaluations, education | Education | Usual care | Low risk of bias |
| Fretheim, 2006 | Tailored intervention to support implementation of CVD guidelines | cRCT | Norway, general practices | Tailored intervention including reminders, audit and feedback and education | Education + audit and feedback | Disease target (BP), adherence (prescription review, chart review) | Low risk of bias |
| Gill, 2009 | EMR-based intervention for lipid management | cRCT | USA, academic family practice | EMR disease management tool | Other (integration into EMR) | Disease target (cholesterol), adherence (chart review) | High risk of bias |
| Goldstein, 2005 | Intervention on drug choice for hypertension | cRCT | Family doctors, nurse practitioners | Education, individual drug profiles, follow up | Education | Disease target (BP), adherence (prescription and chart review) | Low risk of bias |
| Harris, 2005 | Teleconferenced educational detailing for diabetes | cRCT | Family doctors | Eight one hour small group educational sessions with opinion leaders | Education | Disease target (HbA1c), adherence (chart review) | High risk of bias |
| Hayes, 2002 | Quality improvement and written feedback for CHF management | cRCT | Hospitals, CHF patients | Education, quality improvement tools from liaisons, chart reminders | Education + audit and feedback | Disease target (ventricular fnx), adherence (chart review) | High risk of bias |
| Headrick, 1992 | Education and feedback strategies to improve compliance with NCEP-PCEP guidelines | RCT | Resident doctors | Lecture, chart reminders; Lecture, patient specific feedback and chart reminder | Education + Other (reminders) | Disease targets (cholesterol), adherence (chart review) | Low risk of bias |
Table 1 Characteristics of included studies (Continued)

| Study | Intervention Description | Study Design | Setting | Target Population | Intervention Details | Duration | Control Group | Outcomes | Bias Risk |
|-------|--------------------------|--------------|---------|-------------------|----------------------|----------|---------------|----------|-----------|
| Hendriks, 2012 | Nurse led guideline based software supported ICCP | RCT | Netherlands, academic center | Nurse specialist educated patients and CDSS | 12 months | Usual care | Mortality, hospitalizations, quality of life, adherence (chart review) | Low risk of bias |
| Kiesling, 2011 | Case based training to optimize hyperlipidemia care | RCT | Sweden, primary health care centres | Case based training seminars and guideline provided | Education | 2 years | Usual care | Mortality, disease target (cholesterol), adherence (prescription review) | High risk of bias |
| Leonardi, 2012 | Multimodal intervention to improve adherence to targets | cRCT | Italy, renal clinics | Education session, follow up and audits | Education + audit and feedback | 3 years | Education and standard care | Mortality, hospitalizations, quality of life, disease target (cholesterol), adherence (prescription/ chart review) | Low risk of bias |
| Levine, 2011 | Multicomponent internet delivered intervention improve CHD guideline adherence | cRCT | Virgin Islands and Puerto Rico, community primary care clinics | Educational cases, guidelines, monthly update, reminders | Education + Other (reminders) | 27 months | Passive dissemination | Disease target (cholesterol), adherence (chart review) | High risk of bias |
| Ornstein, 2004 | Multimethod quality improvement intervention for adherence to quality indicators in CVD and stroke | cRCT | USA, primary care practices | Education, performance reports quarterly, practice site visits and network meetings (6–7 1–2 day visits) with pharmacist (academic detailing) | Education + academic detailing | 2 years | Education, performance reports quarterly | Disease target (BP), adherence (prescription, chart review) | High risk of bias |
| Petersen, 2013 | Effect of financial incentives to reward guideline based hypertension care | cRCT | USA, primary care clinics | Physician level incentives; practice levels incentives; combined (both) incentives | Other (incentives) | 20 months | Usual care | Disease target (BP), adherence (prescription, chart review) | High risk of bias |
| Peters-Klimm, 2009 | Educational model for GPs for the management of CHF | cRCT | Germany, general practitioner clinics | “Train the trainer” = multidisciplinary andragogic and didactic educational sessions | Education + Other (feedback) | 7 months | Single educational session by cardiologist | Mortality, hospitalizations, quality of life, disease target (course), adherence (prescription review) | Low risk of bias |
| Reutens, 2012 | Education of GPs on the IDF-WPR guidelines to improve metabolic control | cRCT | Asia-Pacific, general practitioner clinics | Education meetings (two 3 months apart), reminder letters and cards, flowsheet on patient notes, patient diabetes passport | Education + Other (reminders, diabetes passport) | 12 months | Instructed on assessments in study but no information on guidelines | Disease target (BP), adherence (chart review) | High risk of bias |
| Rood, 2005 | Computer based guidelines to improve nurse measurement of patient glucose | RCT | The Netherlands, teaching hospital | Guideline based advice via computer decision support software | Other (decision support tool) | 10 weeks | Paper based guideline flowchart | Disease target (glucose), adherence (chart review) | High risk of bias |
Table 1: Characteristics of included studies (Continued)

| Study, Year | Intervention Description                                                                 | Study Design | Study Population                                      | Study Location | Intervention Details                                                                 | Follow-up | Control Group | Disease Target(s)                                                                 | Risk of Bias |
|------------|------------------------------------------------------------------------------------------|--------------|-------------------------------------------------------|----------------|--------------------------------------------------------------------------------------|-----------|----------------|---------------------------------------------------------------------------------|-------------|
| Rossi, 1997| Guideline reminders to improve prescribing based on JNC V guideline                      | cRCT         | Nurse practitioners, hypertension patients            | USA, GIM clinic | Guideline reminder for prescription and alternatives                                 | 5 months  | Usual care     | Disease target (BP), adherence (prescription review)                           | High         |
| Roumie, 2006| Multifactorial intervention to improve quality of care of hypertension patients          | cRCT         | Physicians and nurse practitioners, hypertension patients | USA, community and hospital clinics | Alert on medical record; Educational sessions and alert on medical record             | 6 months  | Providers received email with guideline | Mortality, hospitalizations, disease target (BP), adherence (prescription review) | High         |
| Simon, 2005 | Academic detailing individually or group to increase diuretic use in hypertension patients | cRCT         | Family doctors, hypertension patients                 | USA, community health plan | Academic detailing meeting one-on-one; small group academic detailing session        | 3 months  | Passive dissemination | Hospitalizations, disease target (BP), adherence (chart review)                      | High         |
| Steyn, 2013 | Structured clinical record and training health care providers to control diabetes and hypertension | cRCT         | Nurses, patients with diabetes and hypertension        | South Africa, community health centres | Structured record with guideline embedded added to patient folders, educational package | 1 year    | Passive dissemination | Disease target (HbA1c), adherence (chart review)                                           | High         |
| Svetkey, 2009 | Intervention to increase physician adherence to BP guideline                              | cRCT         | Physicians, hypertension patients                      | USA, community practice | CME courses, treatment algorithm, quarterly feedback on adherence                      | 18 months | Usual care     | Disease target (BP), adherence (chart review)                                           | Low          |
| Tierney, 2003 | Decision support system with guideline for managing ischemic heart disease and CHF patients | RCT          | Pharmacists, CHF patients                              | USA, academic primary care practice | Physicians received patient specific feedback; pharmacist system to send feedback to physicians; both | 1 year    | Usual care     | Mortality, hospitalizations, quality of life, adherence (chart review)                      | High         |
| Van Bruggen, 2008 | Facilitator enhanced multifaceted intervention for T2D guideline implementation          | cRCT         | Family doctors and nurses and practice assistants, T2D patients | The Netherlands, primary care practices | Facilitators visited twice a month to train staff on guidelines, performance feedback | 1 year    | Usual care     | Disease target (HbA1c), adherence (prescription and chart review)                           | Low          |
| Van Steenkiste, 2007 | Decision support tool for risk management improving CVD guideline performance          | cRCT         | Family doctors, patients without CVD                  | The Netherlands, hospital | Education, decision support tool, Other (decision support tool) | 8 months  | Educational materials on guideline | Disease target (lifestyle), adherence (chart review)                                           | High         |
| Verweij, 2013 | Effectiveness of guideline based care on weight, CVD risk                                | cRCT         | Occupational physicians                               | The Netherlands, occupational medicine | Environment scan, patient counselling training, patient toolkit | 18 months | Usual care     | Quality of life, disease target (BP), adherence (chart review)                           | High         |

Footnote: * Risk of bias rated as high or low risk of bias based on overall domains, where high risk of bias designated if greater than 3 domains rated as high risk of bias.
The pooled odds ratio was 2.36 (95 % CI 0.86 to 6.51) before studies with high risk of bias were excluded, and 3.65 (95 % CI 0.53 to 25.15) after studies with high risk of bias were excluded.

We compared results in studies that targeted physicians only in their intervention to interventions that involved non-physician healthcare providers alone or in addition to physicians with subgroup analysis. This subgroup analysis was possible in seven comparisons, and the subgroups of physician participants alone frequently had less heterogeneity than when grouped with all studies, suggesting participants may be a source of heterogeneity (Additional file 2: Figure S1). Another subgroup analysis we conducted compared results in studies that focused on an acute cardiovascular condition to a chronic cardiovascular condition. Five comparisons showed inconsistent results although the heterogeneity was reduced in at least one of the two subgroups in all comparisons.

**GRADE summary of findings tables**
The overall quality of evidence identified in this systematic review was moderate to very low due to high risk of bias, imprecision, and heterogeneity (Table 2). The most patient important outcome of mortality had moderate quality of evidence associated, indicating the results may be interpreted with some confidence.

**Discussion**

**Statement of principal findings**
We have focused on interventions aimed at improving adherence to CVD guidelines. Overall studies are variable in their conclusions on whether the intervention was effective, though our quantitative analysis supports that interventions trend towards having an impact on adherence to guidelines and patient outcomes. One comparison of an education intervention for the adherence outcome was statistically significant, indicating this area of study deserves further consideration, as these interventions may help improve both adherence to guidelines, and more importantly, patient outcomes. Our results were robust where sensitivity analyses were possible. Subgroup analyses (participant and condition) reduced the statistical heterogeneity but there was inconsistency in the subgroup with the larger effect for each analysis. In some cases, the physician subgroup favoured the intervention to a greater degree than the non-physician subgroup, but in other comparisons the opposite was true. The same results were found for the condition subgroup (acute vs. chronic condition). The confidence in these recommendations ranged from moderate to very low based on a GRADE summary of findings due to imprecision, risk of bias, and inconsistency.
Strengths and weaknesses of the review

Our systematic review has several strengths, including that it was comprehensive in inclusion of studies. We included all types of healthcare providers in order to illustrate the impact these interventions can have on both physicians and non-physicians, which is increasingly important for multidisciplinary teams required for complex diseases such as CVD. We limited our study inclusion to those that reported both adherence and a patient outcome, as interventions must improve both in order to be clinically useful. All screening, data extraction, and risk of bias assessment was done in duplicate with trained reviewers to ensure the reproducibility of these results. Our quantitative analysis was pre-specified to avoid finding spurious results due to post hoc analyses. We minimized the number of comparisons that were made while ensuring comparisons had fairly good clinical homogeneity to maintain the strength of those conclusions. We also contacted authors for missing data and to verify the accuracy of our data extractions of their trial, thus we have confidence in this data.

However, this review has limitations. The first relates to the quality of reporting in trials. Reporting of risk of bias domains was poor in many trials, making it difficult to assess risk of bias. There was also significant heterogeneity in the studies’ interventions and characteristics making combining results in a meta-analysis difficult, leading to small numbers of studies included in each comparison. Meta-analyzing results was further complicated by uncertainty of the exact nature of some interventions due to limited descriptions of interventions available in publications. This also limited our
ability to assess publication bias, so we were unable to
determine the effect that might have on our confidence
in these results.

Comparison to similar reviews
A systematic review on CVD guideline implementation
strategies in primary care physicians by Unverzagt et al.
reported similar conclusions on the effectiveness of
education and reminder system interventions to im-
prove adherence [9]. Our review extends these findings,
illustrating the impact at the patient level on mortality,
hospitalizations, quality of life and disease targets, and
to different healthcare providers.

Similar to our findings, a review by Grimshaw et al.
on guideline implementation noted overall the most
effective interventions tend to include specific educa-
tional interventions and patient specific reminders at
point of care [6].

Meaning of the review results
These results indicate there is some evidence to support
the use of some interventions to improve healthcare
provider adherence to CVD guidelines. Despite the limi-
tations in the studies in this review, a trend of interven-
tions improving adherence and patient outcomes was
noted, supporting that these interventions may be more
effective than passive guideline dissemination strategies.
However, more studies are needed to strengthen these
conclusions.

The majority of interventions included were multifa-
ceted, which some reviews have suggested provide posi-
tive outcomes more frequently than single interventions
[53–55]. However, our results were not consistent with
these; we found these interventions have limited effects,
which may be related to the number of components in a
given intervention, as only two interventions included all
of the types of interventions. A review by Squires et al.
found there is ambiguity in the evidence of whether
multifaceted interventions are more effective than single
interventions, which is in agreement with our inconsist-
ent findings [55].

Another possible reason for the overall small effect
sizes may relate to the complexity of the management
of CVD. This includes treating and preventing multiple

![Fig. 5](image_url) Summary disease target outcome forest plot for three comparisons measured by standardized mean difference, with point estimate and 95% CIs

![Fig. 6](image_url) Summary adherence outcome forest plot for five comparisons measured by odds ratio, with point estimates and 95% CIs
| Outcomes   | Illustrative comparative risks$^a$ (95 % CI)                                                                 | Relative effect (95 % CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|------------|-------------------------------------------------------------------------------------------------------------|---------------------------|-----------------------------|---------------------------------|----------|
| Mortality  | Study population                                                                                            | OR 0.54                   | 2190                        | ⚫⚫⚫⚫                              | moderate$^c$ |
| Follow-up: median 6 months | 40 per 1000                                                                                                      | (0.2 to 1.42)            | (3 studies)         |                                  |          |
|            | Moderate                                                                                                     | 26 per 1000               | (5 to 37)$^b$              |                                  |          |
| Disease Targets | The mean disease targets in the intervention groups was 0.32 standard deviations lower                               | 2145                      | (6 studies)            | very low$^{c,ef}$                | SMD −0.32 (−0.71 to 0.07) |
| Follow-up: 3–6 months |                                                                                                               | (0.71 lower to 0.07 higher) |                                  |                                  |          |
| Adherence  | Study population                                                                                            | OR 1.05                   | 6019                        | ⚫⚫⚫⚫                              | low$^a$  |
| Follow-up: 6–24 months | 182 per 1000                                                                                                     | (0.11 to 1.98)           | (4 studies)         |                                  |          |
|            | Moderate                                                                                                     | 146 per 1000              | (18 to 253)$^b$            |                                  |          |
| Hospitalizations | Study population                                                                                        | OR 0.88                   | 979                         | ⚫⚫⚫⚫                              |          |
| Follow-up: 7–22 months | 188 per 1000                                                                                                     | (0.54 to 1.41)           | (4 studies)         |                                  |          |
|            | Moderate                                                                                                     | 191 per 1000              | (113 to 250)$^b$           |                                  |          |
| Disease Targets | The mean disease targets in the intervention groups was 0.09 standard deviations lower                               | 2732                      | (5 studies)            | low$^{fh}$                       | SMD −0.09 (−0.24 to 0.07) |
| Follow-up: 7–27 months | (0.24 lower to 0.07 higher)                                                                                                |                                  |                                  |                                  |          |
| Adherence  | Study population                                                                                            | OR 1.05                   | 6019                        | ⚫⚫⚫⚫                              | low$^{c,ij}$ |
| Follow-up: 7–27 months | 609 per 1000                                                                                                     | (0.82 to 1.34)           | (8 studies)         |                                  |          |
|            | Moderate                                                                                                     | 236 per 1000              | (202 to 293)$^b$           |                                  |          |
| Adherence  | Study population                                                                                            | OR 2.36                   | 2145                        | ⚫⚫⚫⚫                              |          |
risk factors in patients, such as diabetes, hypertension and dyslipidemia [56]. Most guidelines address only one of these diseases, and this may contribute to the small improvements found in this review. Given the multifactorial nature of CVD, it needs to be treated with guidelines that acknowledge this. Using harmonized CVD guidelines such as C-CHANGE is an important step that needs to be taken in CVD guideline implementation intervention trials to ensure the best, most comprehensive care is provided to patients [1]. This is also an important consideration as to why CVD guideline implementation strategies must differ from strategies used in treating simpler diseases such as pneumonia or asthma [57, 58].

Unanswered questions and future research

It would be beneficial for more high quality studies on this topic to be conducted to improve the strength of our recommendations, given the low confidence in most of these estimates due to a small number of studies included in each MA. Interventions should be fully described so they are not only reproducible, but future reviews are able to confidently determine homogeneous groups for meta-analyses. Future reviews on this topic should also define clinically important differences to determine whether the effects are not only statistically significant, but clinically significant as well.

Conclusions

Interventions to improve adherence to CVD guidelines can be effective at improving both adherence and patient outcomes, and are often more effective than guideline dissemination alone. Interventions that focused on healthcare provider education demonstrated statistically significant improvements. The overall quality of evidence available in this review was low, but several patient important outcomes including mortality were supported by moderate to high quality evidence.

Table 2 Summary of findings table for educational interventions (Continued)

| Follow-up: median 6 months | 288 per 1000 489 per 1000 | (0.86 to 6.51) (5 studies) very low\(^a\)
|---------------------------|---------------------------|-------------------|
| Moderate                   | 326 per 1000 533 per 1000 | (294 to 759)\(^b\) |

\(^a\)The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI)

\(^b\)Assumed Risk is based on the default calculation within GRADEpro (mean control group risk, and median control group risk)

Abbreviations

CVD: Cardiovascular disease; CPG: Clinical practice guideline; MA: Meta-analysis; RCT: Randomized controlled trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; CME: Continuing medical education; OR: Odds ratio; SMD: Standardized mean difference; CI: Confidence interval.

Competing Interests

CVZ received a research grant through Boehringer-Ingelheim. All other authors declare no conflicts of interest.

Authors’ contributions

RAJ conceived of the study and its design, coordinated and participated in data extraction and carried out statistical analyses, and drafted the manuscript. MJT participated in screening and data extraction. CT participated in screening. AC participated in data extraction and carried out statistical analysis. RAJ helped plan the design and data analysis, and helped draft the manuscript. All authors read, revised, and approved the final manuscript.

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Availability of data and materials
Not applicable.

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