Cardiovascular medication: improving adherence

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ABSTRACT

INTRODUCTION: Adherence to medication is generally defined as the extent to which people take medications as prescribed by their healthcare providers. It can be assessed in many ways (e.g., by self-reporting, pill counting, direct observation, electronic monitoring, or by pharmacy records). This review reports effects of intervention on adherence to cardiovascular medications however adherence has been measured. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of interventions to improve adherence to long-term medication for cardiovascular disease in adults? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 39 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: patient health education, prescriber education, prompting mechanisms, reminder packaging (calendar [blister] packs, multi-dose pill boxes), and simplified dosing.

QUESTIONS

INTERVENTIONS

INTERVENTIONS TO IMPROVE ADHERENCE TO CARDIOVASCULAR MEDICATION

Key points

- Adherence to medication is generally defined as the extent to which people take medications as prescribed by their healthcare providers.

  It can be assessed in many ways (e.g., by self-reporting, pill counting, direct observation, electronic monitoring, or through pharmacy records). In this review, we have reported adherence to cardiovascular medications however it has been measured.

- The RCTs we found used a variety of different interventions in different populations, measured adherence differently, and expressed and analysed results differently.

  The diversity and complexity of interventions employed in RCTs makes it difficult to separate out any individual components that might be of benefit.

- We found evidence that simplified dosing regimens may increase adherence compared with more complex regimens.

  While simplifying the frequency of dosage may increase adherence, it is not known whether simplified regimens may increase adherence when someone is taking multiple drugs, as may be the case with cardiovascular medicines.

  In altering a drug regimen simply to increase adherence, any changes could potentially affect the effectiveness of the treatment, and could also potentially increase adverse effects.

- Prompting mechanisms may also increase adherence to medication.

  Some prompting mechanisms may be simple and inexpensive (e.g., mailed reminders), while others (e.g., daily telephone calls, installing videophones) seem impracticable for use in routine practice.

- Patient health education may also increase adherence to medication but more data are needed to draw conclusions.

  Adherence behaviour is complex. Traditional education methods may fail to address this. However, more patient-centred approaches, particularly those that are nurse- or pharmacist-led, using video or telephone strategies, may be beneficial and require further investigation.

  We found some evidence that a combination of strategies, such as education plus prompting, may be more successful than a single educational strategy.

- We found no evidence from one RCT that reminder packaging (a calendar blister pack) was effective, and found insufficient evidence on other types of reminder packaging such as multi-dose pill boxes.

- We found one RCT of prescriber education in a developing country, which showed that a 1-day intensive training session of general practitioners on hypertension improved medication adherence compared with usual care but

these data are not generalisable to the range of people taking cardiovascular medication so we cannot draw firm conclusions about this intervention.

DEFINITION

Definition of adherence: Adherence to a medication regimen is generally defined as the extent to which people take medications as prescribed by their healthcare providers. [1] Adherence, compliance, and concordance are often used interchangeably when studying health behaviour, but their meanings are in fact different, particularly in the context of RCTs examining interventions aimed at improving adherence. Adherence takes into account that people choose to take their medicines, have control over their use, and develop an agreement with healthcare professionals about their management. [2] The main difference between the terms "adherence" and "compliance" is on a motivational level, with the latter suggesting that the patient is passively following the physician's orders, and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the physician. [1] Unfortunately, the term "concordance" has occasionally, and not always appropriately, replaced the terms "compliance" or "adherence". [3] "Concordance" aims to describe an agreement between patient and healthcare professional about the whole process of medication-taking as part of a wider consultation, rather than describing the specific extent to which medication is taken. [4] For the purposes of this review, "adherence" will be defined as the extent to which people take medications as prescribed by their healthcare providers. The reporting of adherence varies, with some studies reporting adherence as a dichotomous outcome, and using an artificial cut-off point (e.g., 80% "adherent"), whereas other studies compare study arms using continuous outcomes (e.g., a count of pills taken of 75% *v* 91%). **Measurement of adherence:** The ideal measurement of adherence should: be usable over a prolonged period; be unobtrusive; be non-invasive; be practicable and cheap; yield immediate results; and not be open to manipulation. [5] Based on these stringent criteria, the objective measurement of adherence is difficult, and poses a challenge for researchers and clinicians. Measurement of adherence can be divided into "direct" (which demonstrate drug ingestion) and "indirect" (which do not demonstrate drug ingestion) methods. Direct methods include observing people taking medication, or the measurement of medicine, metabolites, or biological markers in the blood. Although objective and accurate, direct adherence measures are often impractical or too expensive for the RCT setting. A variety of indirect adherence measures are commonly employed in RCTs, and each one has strengths and weaknesses. These include self-reporting by patients, prescribing data, pill counting, measurement of physiological markers, and electronic monitoring. Patient self-reporting of adherence is simple, inexpensive, and probably the most practical and useful in the clinical setting. It is, however, subject to considerable bias, as the person may wish to please the investigator, be worried about admitting to not taking medication, or simply not accurately remember. Prescribing data, such as the rate of prescription refills or cessation of refills (discontinuation rate), are easy to obtain through pharmacies, but require a closed-pharmacy system to be accurate, and cannot be regarded as equivalent to ingestion of medication. However, this information affords a useful proxy, and may be easier to measure over long follow-up periods. [6] Pill counts provide a direct measure of adherence. However, they may be manipulated by people if they are aware that the pills are being counted (e.g., pill dumping), and it does not necessarily mean that medication has been taken at the correct time. Measurement of physiological markers (e.g., measuring heart rate in patients taking beta-blockers) is easy to perform, but is greatly limited by its assumption of a cause-and-effect relationship, which is rarely applicable. Electronic monitoring methods have greatly advanced recently and allow recordings of the timing and frequency of drug ingestion, which make them the only method to provide data on drug-taking patterns. However, they are expensive, and there is no guarantee that opening of the medication container is followed by ingestion of the correct dose. It could also be argued that placing an electronic cap to measure compliance is an intervention in itself as people are aware that they are being monitored (Hawthorne effect). [7] This effect may or may not persist in the longer term when people become used to the electronic cap. Although electronic monitoring is closest to a "gold standard" in measuring adherence, it has so far been used mainly as a research tool owing to its relatively high cost.

INCIDENCE/ PREVALENCE

Not applicable for this review.

AETIOLOGY/ RISK FACTORS

The reasons for not adhering to prescribed cardiovascular medication are complex, and non-adherence may lead to various sequelae. For example, the prescribing clinician may alter or discontinue a regimen believing it not to be working when, in fact, it may have been taken only inconsistently or not at all. Failure to adhere to a prescribed regimen may increase adverse effects from the regimen, in that medication is taken incorrectly, and may fail to improve symptoms from the underlying condition for which it was prescribed. **Interventions to improve adherence:** Interventions to improve adherence can potentially be divided into a variety of different categories or groupings. In this review we have grouped RCTs under the categories of: prescriber education; prompting mechanisms; patient health education; simplified dosing; and reminder packaging (blister packs and pill boxes), and have explained what we have included under each category where necessary. However, inter-

ventions to improve adherence are complex by nature and will often be combined in a multi-factorial or "complex intervention" approach. This approach is necessary as there are many factors that contribute to poor adherence, although this does make it difficult to tease out the individual components of many adherence interventions. Educational interventions can be directed at prescribers, patients, and their family members using written material, videotapes, or individual or group training. Prompting mechanisms are intended to stimulate medication-taking through mailed or telephoned reminders or through the use of electronic medication-reminder caps. Simplified dosing is intended to improve adherence through the reduction of dosing frequency (e.g., once-daily regimens *v* twice-daily regimens, or twice-daily regimens *v* 3-times-daily regimens). Reminder packaging falls into two distinct categories: those that are packaged in pill boxes (multi-compartment compliance aid, dose administration aid) or those that are pre-packaged into blister packs (calendar blister, unit dose, monitored dosage system). Definitions of terms relating to reminder packaging are reported in table 1, p 30 .

PROGNOSIS

Patterns of medication-taking behaviour and adherence: Patterns of medication-taking behaviour have been accurately described using electronic monitoring devices. Six general patterns of taking medication emerge among people treated for chronic illnesses who continue to take their medications: approximately one sixth come close to perfect adherence to a regimen; one sixth take nearly all doses, but with some timing irregularity; one sixth miss an occasional single day's dose and have some timing inconsistency; one sixth take drug holidays three to four times a year, with occasional omissions of doses; one sixth have a drug holiday monthly or more often, with frequent omissions of doses; and one sixth take few or no doses while giving the impression of good adherence. [8] [9] Most deviations in taking medication occur as omissions of doses (rather than additions) or delays in the timing of doses. [10] [11] Levels of adherence are poorly described, with those studies of higher quality limited by smaller numbers, and those studies of larger populations limited by crude measures of adherence. However, in terms of adherence to cardiovascular medication, most studies have examined adherence in relation to lipid-lowering drugs. It is evident that target cholesterol concentrations are only achieved in less than 50% of people receiving lipid-lowering drugs, and that only one in four people continue taking cholesterol-lowering drugs long term. [12] [13] In adherence studies of people without CHD taking lipid-lowering drugs for the purposes of primary prevention, discontinuation rates are higher compared with people taking lipid-lowering drugs for the purpose of secondary prevention, indicating a possible relationship between adherence and awareness of illness. [14] [15]

AIMS OF INTERVENTION

To increase adherence to cardiovascular medication in order to achieve treatment goals; to prevent relapse of disease; to reduce morbidity; to reduce mortality; to improve quality of life, with minimal adverse effects.

OUTCOMES

Adherence to medication, however measured. Adherence is often measured by pill count, prescription renewal requests, self-reporting, and electronic monitoring. **Adverse effects**.

METHODS

Clinical Evidence search and appraisal April 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to April 2010, Embase 1980 to April 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 3 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, undertaken in adults. Further studies were identified from a search of bibliographies of identified systematic reviews. We included RCTs whatever the level of blinding (whether double-blind, single-blind, or open). RCTs had to contain at least 20 people in total, or at least 10 per study arm, of whom more than 80% were followed up. The minimum length of follow-up required to include studies was 6 weeks. We have included RCTs in people with CVD and excluded RCTs in mixed populations (i.e., RCTs that also included people with other diseases, in which people with CVD did not form the majority). We excluded RCTs in hospitalised people, and included RCTs in people in the community or seen as outpatients, who were responsible for administering their own medication. Difficulties in evaluating RCTs included analysing a multiplicity of different interventions and combinations of different elements that were not easily categorised. Therefore, in each treatment option, we have explicitly stated what we have included under that option heading. We have excluded RCTs that employed complex interventions (i.e., mixtures of different elements) in which the individual effects of our intervention of interest could not be separately assessed. We have also excluded RCTs that did not

directly report adherence as an outcome, or reported an adherence outcome that was not clearly defined. There was a wide variation between RCTs in how adherence was measured (e.g., whether by pill count, self-reporting, electronic methods, or the number of repeat prescriptions obtained), with no standard method employed. We have therefore included RCTs however adherence was measured, but explicitly stated the adherence outcome measure employed in each RCT. We identified a number of systematic reviews that employed different inclusion criteria, and that categorised interventions in different groupings. The systematic reviews did not pool data because of differences between included RCTs (including study designs, interventions employed, and outcome measures assessed). We have therefore reported each of the RCTs included in the systematic reviews separately. Measures to increase adherence may or may not have adverse effects (e.g., regular contact and stressing the importance of medication and possible adverse effects of non-compliance may increase anxiety in some people). For adverse events we have reported harms data relating directly to the adherence intervention employed. We have not reported harms data relating to the drug treatments used, as adherence is our outcome of interest. The exception to this is in the simplified-dosing option, where we have reported drug adverse effects, as the intervention directly alters the drug regimen (e.g., to once-daily dosage, rather than twice-daily). Hence, in this case, differences in drug adverse effects between the regimens are due to the adherence intervention itself. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 31). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions to improve adherence to long-term medication for CVD in adults?**

OPTION **PROMPTING MECHANISMS**

- For GRADE evaluation of interventions for Cardiovascular medication: improving adherence, see table, p 31 .
- Prompting mechanisms may increase adherence to medication.
- Some prompting mechanisms may be simple and inexpensive (e.g., mailed reminders), while others (e.g., daily telephone calls, installing videophones) seem impracticable for use in routine practice.

Benefits and harms

Prompting mechanisms versus usual care:

We found 11 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] [20] 2003; [21] [22] 2004; [23] 2007; [24] 2008; [25] 2009 [26]), which identified 5 RCTs of sufficient quality. [7] [27] [28] [29] [30] The reviews did not pool data. Some of the RCTs had weak methods, and completeness of reporting varied widely among trials. Adherence was measured in a variety of ways in the 5 RCTs (pill counts, pharmacy refill records, electronic caps) and overall compliance was calculated in different ways, with no standard method employed. For full details of prompting mechanisms used in RCTs, see further information on studies.

Adherence to medication

Compared with usual care Prompting interventions (including daily and weekly telephone calls, video-telephone calls, mailed reminders, and electronic medication-reminder caps) may be more effective than usual care at improving adherence in people taking cardiovascular medication. However, the practicality of some of these interventions in routine clinical practice is unclear (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to medication					
[7] RCT	60 people age 65 years or older, diagnosis of chronic heart failure, had	**Compliance (baseline to post-intervention) monitored by electronic caps on medication bottles , 6-week intervention**	P <0.05 among groups Direct statistical analysis of telephone group or video-telephone		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	to have telephone socket, home not in high-crime area, Mini-Mental State Examination (MMSE) score of 20 or better.	**phase followed by 2-week post-intervention compliance monitoring period** 76% to 74% with daily telephone calls 82% to 84% with daily video-telephone calls 81% to 57% with usual care Absolute numbers not reported	group versus usual care not reported, but higher rates of adherence in prompting mechanism groups		
[27] RCT	70 people with hypertension on long-term treatment, age 50 years or older, on one or more drugs	**Mean % compliance (defined as doses consumed/doses prescribed x 100) , number of remaining doses in each vial counted at 12 weeks** 95% with electronic cap on medication vial 78% with standard cap Absolute numbers not reported	P = 0.0002	○○○	prompting intervention (electronic cap)
[28] RCT	30 people with CABG or PTCA in the last 7 to 30 days, baseline fasting LDL 130 mg/dL or higher, on lovastatin and colestipol, with a telephone in their home	**Compliance (measured by pill and packet counts) , 6 weeks** 92% for lovastatin and 93% for colestipol with telephone call 89% for lovastatin and 90% for colestipol with no telephone call Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[28] RCT	30 people with CABG or PTCA in the last 7 to 30 days, baseline fasting LDL 130 mg/dL or higher, on lovastatin and colestipol, with a telephone in their home	**Compliance (measured by pill and packet counts) , 12 weeks** 88% for lovastatin and 90% for colestipol with telephone call 86% for lovastatin and 88% for colestipol with no telephone call Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[28] RCT	30 people with CABG or PTCA in the last 7 to 30 days, baseline fasting LDL 130 mg/dL or higher, on lovastatin and colestipol, with a telephone in their home	**Compliance (measured by contacting pharmacies to obtain document refill information) , 1 year** 71% for lovastatin and 54% for colestipol with telephone call 47% for lovastatin and 27% for colestipol with no telephone call Absolute numbers not reported	P <0.05	○○○	prompting intervention (telephone call)
[28] RCT	30 people with CABG or PTCA in the last 7 to 30 days, baseline fasting LDL 130 mg/dL or higher, on lovastatin and colestipol, with a telephone in their home	**Compliance (measured by contacting pharmacies to obtain document refill information) , 2 years** 63% for lovastatin and 48% for colestipol with telephone call 39% for lovastatin and 23% for colestipol with no telephone call Absolute numbers not reported	P <0.05	○○○	prompting intervention (telephone call)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[29] RCT **3-armed trial**	311 people on cardiovascular medications, attended primary care or speciality clinic at a university health centre, medication refill due in 2 days, people selected from a computer database Third arm evaluated telephone reminder	**Mean compliant events, which equalled the number of refills divided by the possible number of refills , outcome measured for 3 months** 0.58 with no reminder 0.65 with postcard reminder 2 working days before medication refill due	P <0.05 Post hoc analysis	○○○	prompting intervention (reminder postcard)
[29] RCT **3-armed trial**	311 people on cardiovascular medications, attended primary care or speciality clinic at a university health centre, medication refill due in 2 days, people selected from a computer database Third arm evaluated postcard reminder	**Mean compliant events, which equalled the number of refills divided by the possible number of refills , outcome measured for 3 months** 0.58 with no reminder 0.64 with telephone call 1 working day before medication refill due	P <0.05 Post hoc analysis	○○○	prompting intervention (telephone call)
[30] RCT **3-armed trial**	636 people with newly diagnosed or uncontrolled mild to moderate hypertension, aged 18 to 80 years, on single therapy	**Mean % compliance (compliance assessed by counting tablets; % compliance defined as total number of consumed tablets/total number of tablets that should have been consumed x 100) , assessed at 5 clinic visits: inclusion visit, and 4 follow-up visits at 26, 52, 106, and 155 days** 90% with usual care 99% with telephone intervention 97% with mailed intervention Absolute numbers not reported	P = 0.0001 for either intervention *v* usual care No direct statistical comparison of telephone intervention alone or mailed intervention alone versus usual care reported, but higher rates of adherence in prompting mechanism groups	○○○	prompting intervention
[30] RCT **3-armed trial**	636 people with newly diagnosed or uncontrolled mild to moderate hypertension, aged 18 to 80 years, on single therapy	**Proportion of compliers (participants with 80–110% drug consumption) (compliance assessed by counting tablets; % compliance defined as total number of consumed tablets/total number of tablets that should have been consumed x 100) , assessed at 5 clinic visits: inclusion visit, and 4 follow-up visits at 26, 52, 106, and 155 days** 69% with usual care 96% with telephone intervention 91% with mailed intervention Absolute numbers not reported	P = 0.0001 for either intervention *v* usual care Between-group analysis No direct statistical comparison of telephone intervention alone or mailed intervention alone versus usual care reported, but higher rates of adherence in prompting mechanism groups	○○○	prompting intervention

Adverse effects

No data from the following reference on this outcome. [7] [27] [28] [29] [30]

Prompting mechanism plus usual care versus unit-of-use packaging plus usual care versus unit-of-use packaging plus prompting mechanism plus usual care versus usual care alone:

We found 11 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] [20] 2003; [21] [22] 2004; [23] 2007; [24] 2008; [25] 2009 [26]), which identified two RCTs of sufficient quality. [6] The reviews did not pool data. The two RCTs were undertaken by the same research group, and employed a similar methodology.

Adherence to medication

Prompting mechanism plus usual care compared with unit-of-use packaging plus usual care compared with unit-of-use packaging plus prompting mechanism plus usual care compared with usual care alone A prompting intervention (mailed reminder 10 days before refill date), unit-of-use packaging, and combined prompting intervention plus unit-of-use packaging may all be more effective than usual care at improving adherence to medication in people with mild to moderate hypertension; and the combined prompting intervention plus unit-of-use packaging may be more effective than the prompting intervention alone or unit-of-use packaging alone. However, the unit-of-use packaging intervention was not fully defined (a 30-day inventory tray in 1 RCT; not defined in another RCT), which makes drawing conclusions on it difficult. We don't know whether a mailed prompting reminder is more effective than unit-of-use packaging at improving adherence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to medication					
[6] RCT **4-armed trial**	304 people, previously untreated mild to moderate hypertension, <65 years old, on verapamil once daily, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care plus unit-of-use packaging and standard care plus mailed reminder plus unit-of-use packaging	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.64 with standard care plus mailed reminder 10 days prior to medication refill date 0.56 with standard care	P <0.05	○○○	prompting intervention (mailed reminder)
[6] RCT **4-armed trial**	304 people, previously untreated mild to moderate hypertension, <65 years old, on verapamil once daily, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care plus mailed reminder 10 days prior to medication refill date and standard care plus mailed reminder plus unit-of-use packaging	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.67 with standard care plus unit-of-use packaging 0.56 with standard care	P <0.05 The unit-of-use packaging was reported to be "a sequentially numbered 30-day supply inventory tray with easy-access compartments" but was not further defined	○○○	reminder packaging (unit-of-use packaging)
[6] RCT **4-armed trial**	304 people, previously untreated mild to moderate hypertension, <65	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication posses-**	P <0.05 The unit-of-use packaging was reported to be "a sequentially numbered 30-day supply inventory tray with easy-access compart-	○○○	prompting mechanism (mailed reminder) plus reminder packaging (unit-of-use packaging)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	years old, on verapamil once daily, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care plus mailed reminder 10 days prior to medication refill date and standard care plus unit-of-use packaging	**sion ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.56 with standard care 0.79 with standard care plus mailed reminder plus unit-of-use packaging	ments" but was not further defined		
[6] RCT **4-armed trial**	304 people, previously untreated mild to moderate hypertension, <65 years old, on verapamil once daily, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care alone and standard care plus mailed reminder plus unit-of-use packaging	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.64 with standard care plus mailed reminder 10 days prior to medication refill date 0.67 with standard care plus unit-of-use packaging	Reported as not significant P value not reported The unit-of-use packaging was reported to be "a sequentially numbered 30-day supply inventory tray with easy-access compartments" but was not further defined	⟷	Not significant
[6] RCT **4-armed trial**	304 people, previously untreated mild to moderate hypertension, <65 years old, on verapamil once daily, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care alone and standard care plus unit-of-use packaging	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.64 with standard care plus mailed reminder 10 days prior to medication refill date 0.79 with standard care plus mailed reminder plus unit-of-use packaging	P <0.05 The unit-of-use packaging was reported to be "a sequentially numbered 30-day supply inventory tray with easy-access compartments" but was not further defined	○○○	prompting mechanism (mailed reminder) plus reminder packaging (unit-of-use-packaging)
[6] RCT **4-armed trial**	304 people, previously untreated mild to moderate hypertension, <65 years old, on verapamil once daily, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care alone and standard care plus mailed reminder 10 days prior to medication refill date	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.67 with standard care plus unit-of-use packaging 0.79 with standard care plus mailed reminder plus unit-of-use packaging	P <0.05 The unit-of-use packaging was reported to be "a sequentially numbered 30-day supply inventory tray with easy-access compartments" but was not further defined	○○○	prompting mechanism (mailed reminder) plus reminder packaging (unit-of-use-packaging)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[31] RCT **4-armed trial**	128 people with previously untreated mild to moderate hypertension, on verapamil once daily, mean age approximately 54 years, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care plus unit-of-use packaging and standard care plus mailed reminder plus unit-of-use packaging	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.71 with standard care plus mailed reminder 10 days prior to medication refill date 0.64 with standard care	P <0.05	○○○	prompting intervention (mailed reminder)
[31] RCT **4-armed trial**	128 people with previously untreated mild to moderate hypertension, on verapamil once daily, mean age approximately 54 years, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care plus mailed reminder 10 days prior to medication refill date and standard care plus mailed reminder plus unit-of-use packaging	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.64 with standard care 0.75 with standard care plus unit-of-use packaging	P <0.05 The unit-of-use packaging was not further defined	○○○	reminder packaging (unit-of-use packaging)
[31] RCT **4-armed trial**	128 people with previously untreated mild to moderate hypertension, on verapamil once daily, mean age approximately 54 years, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care plus mailed reminder 10 days prior to medication refill date and standard care plus unit-of-use packaging	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.87 with standard care plus mailed reminder plus unit-of-use packaging 0.64 with standard care	P <0.05 The unit-of-use packaging was not further defined	○○○	prompting mechanism (mailed reminder) plus reminder packaging (unit-of-use-packaging)
[31] RCT **4-armed trial**	128 people with previously untreated mild to moderate hypertension, on verapamil once daily, mean age approximately 54 years, refill medication dispensed in 30-day supplies The remaining arms evaluated	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)**	Reported as not significant P value not reported The unit-of-use packaging was not further defined	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	standard care alone and standard care plus mailed reminder plus unit-of-use packaging	0.71 with standard care plus mailed reminder 10 days prior to medication refill date 0.75 with standard care plus unit-of-use packaging			
[31] RCT **4-armed trial**	128 people with previously untreated mild to moderate hypertension, on verapamil once daily, mean age approximately 54 years, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care alone and standard care plus unit-of-use packaging	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.71 with standard care plus mailed reminder 10 days prior to medication refill date 0.87 with standard care plus mailed reminder plus unit-of-use packaging	P <0.05 The unit-of-use packaging was not further defined	○○○	prompting mechanism (mailed reminder) plus reminder packaging (unit-of-use-packaging)
[31] RCT **4-armed trial**	128 people with previously untreated mild to moderate hypertension, on verapamil once daily, mean age approximately 54 years, refill medication dispensed in 30-day supplies The remaining arms evaluated standard care alone and standard care plus mailed reminder 10 days prior to medication refill date	**Mean number of days' supply of medication obtained over 360-day study period, expressed as "medication possession ratio" (defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied)** 0.75 with standard care plus unit-of-use packaging 0.87 with standard care plus mailed reminder plus unit-of-use packaging	P <0.05 The unit-of-use packaging was not further defined	○○○	prompting mechanism (mailed reminder) plus reminder packaging (unit-of-use-packaging)

Adverse effects

No data from the following reference on this outcome. [31] [6]

Prompting mechanism plus patient health education versus usual care:

We found 11 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] [20] 2003; [21] [22] 2004; [23] 2007; [24] 2008; [25] 2009 [26]), which identified one RCT of sufficient quality. [32] See further information on studies for full details on interventions.

Adherence to medication

Compared with usual care A prompting intervention (including a telephone call and mailed reminder) plus patient health education (including an educational programme, newsletter, and general health advice) may be more effective than usual care at improving adherence to medication in people with newly diagnosed hypertension and in people with existing hypertension at 1 year (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to medication					
[32] RCT	453 outpatients, mild to moderate hypertension, on once-daily atenolol, either new cases or existing (previously treated); subgroup analysis of 344 people with existing hypertension Subgroup analysis	**Results expressed as medication possession ratio (defined as mean number of days' supply of medication obtained over 360-day trial period) , follow-up at 6 months** 0.82 with prompting intervention plus patient health education 0.48 with usual care	P <0.05	○○○	prompting intervention plus patient health education
[32] RCT	453 outpatients, mild to moderate hypertension, on once-daily atenolol, either new cases or existing (previously treated); subgroup analysis of 109 people with new hypertension Subgroup analysis	**Results expressed as medication possession ratio (defined as mean number of days' supply of medication obtained over 360-day study period) , follow-up at 6 months** 0.93 with prompting intervention plus patient health education 0.52 with usual care	P <0.05	○○○	prompting intervention plus patient health education

Adverse effects

No data from the following reference on this outcome. [32]

Prompting mechanisms versus prescriber education, patient health education, or simplified dosing:

We found 11 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] [20] 2003; [21] [22] 2004; [23] 2007; [24] 2008; [25] 2009 [26]), which identified no RCTs of sufficient quality.

Further information on studies

[7] **Prompting mechanism** Daily calls, which lasted 3 to 5 minutes and were made by research assistant on Monday to Friday. **RCT methods** Method of randomisation was described. Results based on 50/60 (83%) of those randomised. Withdrawals in each individual group not reported. Participants offered $20 to take part in study. Electronic caps placed on maximum of 4 medication bottles for each person. No significant difference in adherence reported between telephone and video-telephone groups (reported as not significant; P value not reported).

[27] **Prompting mechanism** Electronic cap on medication bottles: digital timepiece displayed when last opened, alarm bleeped when dose due, flashed when dose missed. **RCT methods** Participants blinded, investigators not blinded. Method of randomisation not described. Loss to follow-up not reported. Blood pressure results were measured but presented as baseline analysis; no between-group analyses reported. Factoral design: only first randomisation reported here.

[28] **Prompting mechanism** Telephone calls: same pharmacist telephoned people in their homes every week for 12 weeks. Standard set of questions, with emphasis on the importance of therapy, and asking reasons for non-compliance where appropriate. **RCT methods** The method of randomisation was described, and follow-up was 100%. Different measures of adherence in short term (up to 12 weeks) and long term (up to 2 years). Small RCT (15 people in each group). Changes in total cholesterol, LDL, HDL, and triglyceride level were not significantly different between groups at 6 or 12 weeks. Compared with the no-telephone group, the telephone inter-

vention significantly reduced total cholesterol (P = 0.03), LDL (P = 0.02), and triglyceride levels (P = 0.04) at 1 and 2 years.

[29] **RCT methods** Method of randomisation not described. Level of blinding not reported. A telephone call was also made to people in all three groups who were 3 days late obtaining the medication. This was to determine: if postcard group had received postcard; if medication obtained at different pharmacy; and reasons for not refilling. Calls made to all groups (including control) may have influenced the results. Of 40/311 (13%) total withdrawals, 35 were in group (1). These people were excluded from analysis as not contacted by telephone (unlisted or telephone disconnected). Hence, withdrawals varied between groups. The RCT found no significant difference between postcard and telephone groups in mean compliant events (P value not reported).

[30] **Prompting mechanism** Telephone intervention: three calls in total by nurses after scheduled visits to reinforce compliance, standard call, with good compliance praised. Mailed intervention: three mailed communications reinforcing compliance, health education, and reminding people of clinic visits. **RCT methods** Method of randomisation was described. Results based on follow-up of 538/636 (86%) people. Significantly superior control of blood pressure with telephone intervention compared with usual care (63% with telephone intervention *v* 47% with usual care; P <0.05).

[6] **RCT methods** Follow-up of 100%. Method of randomisation not described. Level of blinding not reported. "Unit-of-use" packaging was reported to be "a sequentially numbered 30-day supply inventory tray with easy-access compartments". It was not further described.

[32] **Prompting mechanism** Active intervention consisted of health education (educational programme, newsletter discussing importance of compliance, nutrition, and lifestyle advice) plus prompting intervention (telephone conversation 1 week prior to next medication refill initially, and then mailed reminder 10 days prior to refill each month). **RCT methods** Method of randomisation not described. Level of blinding not described.

Comment:

Clinical guide:
As outlined above, there is a variety of potential prompting mechanisms, from the simple and relatively low-cost mailed reminder to the more expensive and labour-intensive use of telephone calls, video-telephone calls, or electronic medication-reminder caps (and we have included RCTs that assessed any form). There is a small amount of evidence for effect with all of the above mechanisms, but several (e.g., daily telephone calls, installing videophones) remain impracticable for use in routine clinical practice.

OPTION SIMPLIFIED DOSING

- For GRADE evaluation of interventions for Cardiovascular medication: improving adherence, see table, p 31 .
- We found evidence that simplified dosing regimens may increase adherence compared with more complex regimens.
- While simplifying the frequency of dosage may increase adherence, it is not known whether simplified regimens may increase adherence when someone is taking multiple drugs, as may be the case with cardiovascular medicines.
- In altering a drug regimen simply to increase adherence, any changes could potentially affect the effectiveness of the treatment, and could also potentially increase adverse effects.

Benefits and harms

Simplified dosing regimens versus more complex regimens:

We found 10 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] 2003; [21] [33] [34] 2004; [23] 2007; [24] 2008 [25]), which identified 6 RCTs of sufficient quality. [35] [36] [37] [38] [39] [40] The reviews did not pool data. We found no subsequent RCTs.

Adherence to medication

Compared with more complex dosing regimens Simplified dosing regimens may be more effective than more complex dosing regimens (e.g., once-daily regimens compared with twice-daily regimens, or twice-daily regimens compared with 3-times-daily regimens) at increasing adherence to medication in people with hypertension, hyperlipidaemia, and angina (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to medication					
[35] RCT	389 people with mild or moderate hypertension, mean age 53 to 54 years, adequately controlled, on metoprolol or propranolol either as monotherapy or in conjunction with diuretic. Participants continued their other medication as normal	**Compliance (defined as those people taking at least 90% of their medications) , assessment by pill count at 6 and 10 weeks during clinic visit** 93% of people with once-daily regimen of metoprolol (slow release) 81.5% of people with twice-daily regimen of metoprolol Absolute numbers not reported 2 weeks of baseline monitoring on original medication, then 8 weeks of intervention	P = 0.009	○○○	simplified dosing
[35] RCT	389 people with mild or moderate hypertension, mean age 53 to 54 years, adequately controlled, on metoprolol or propranolol either as monotherapy or in conjunction with diuretic. Participants continued their other medication as normal	**Tablet count compliance over test period, expressed as mean rank , assessment by pill count at 6 and 10 weeks during clinic visit** 123.38 with once-daily regimen of metoprolol (slow release) 100.92 with twice-daily regimen of metoprolol Absolute numbers not reported 2 weeks of baseline monitoring on original medication, then 8 weeks of intervention	P = 0.0089	○○○	simplified dosing
[36] RCT	7274 people with hypertension, suitable for treatment with nicardipine, age 18 years and older, mean age 50 years, 60% on current treatment. Other concomitant antihypertensive therapies allowed	**Self-reported — participants asked to rate their compliance (results presented as self-reported compliance of 100%, 80%, or 0% to 60%) , adherence assessed at 3 months by standardised interview** 82%, 15%, and 3% with nicardipine twice daily (slow release) 71%, 24%, and 4% with nicardipine 3 times daily Absolute numbers not reported	RCT reported that "all the differences were statistically significant, P <0.001"	○○○	simplified dosing
[37] RCT **Crossover design** Intervention continued for 8 months, then groups were crossed over for further 8 months	29 men, participants in earlier study, mean age 49 years, on niacin 4 times daily plus lovastatin twice daily plus colestipol twice daily for 1 year, adjusted to maintain target cholesterol 150 to 175 mg/dL, high risk of cardiac events (elevated apoprotein B or stenosis or strong family history). Other medication (lovastatin and colestipol) continued as before	**Compliance calculated using computer that accounted for drug supplies given, the recommended dosage, and a count of returned medication; expressed as % of dose recommended** 96% with niacin twice daily 85% with niacin 4 times daily Absolute numbers not reported	P = 0.01	○○○	simplified dosing

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[38] RCT	31 people with stable angina, mean age 63 to 64 years (range 47–74 years)	**Manual pill count (tablets consumed, % of correct number) , follow-up at 12 weeks** 98% with isosorbide mononitrate once daily 98% with isosorbide mononitrate twice daily Absolute numbers not reported	Significance not assessed P value not reported		
[38] RCT	31 people with stable angina, mean age 63 to 64 years (range 47–74 years)	**Compliance assessed by electronic bottle cap that measured date and time bottle opened (outcome expressed as % of days with correct number of openings) , follow-up at 12 weeks** 97% with isosorbide mononitrate once daily 88% with isosorbide mononitrate twice daily Absolute numbers not reported	P <0.05	○○○	simplified dosing
[38] RCT	31 people with stable angina, mean age 63 to 64 years (range 47–74 years)	**Compliance assessed by electronic bottle cap that measured date and time bottle opened (outcome expressed as the % of intervals between openings within the correct time range) , follow-up at 12 weeks** 88% with isosorbide mononitrate once daily 69% with isosorbide mononitrate twice daily Absolute numbers not reported	P <0.05	○○○	simplified dosing
[39] RCT **Crossover design** Given initial treatment for 4 weeks, then groups crossed over	27 people, mild hypertension, well controlled on monotherapy, mean age 62 years	**Compliance assessed by pill count (outcome expressed as % of doses taken) , follow-up at 8 weeks (after crossover)** with enalapril once daily with enalapril twice daily Absolute results not reported	P <0.01	○○○	simplified dosing
[39] RCT **Crossover design** Given initial treatment for 4 weeks, then groups crossed over	27 people, mild hypertension, well controlled on monotherapy, mean age 62 years	**Compliance assessed by electronic bottle cap (outcome expressed as % of doses taken by electronic count) , follow-up at 8 weeks (after crossover)** with enalapril once daily with enalapril twice daily	P <0.001	○○○	simplified dosing
[39] RCT **Crossover design** Given initial treatment for 4 weeks,	27 people, mild hypertension, well controlled on monotherapy, mean age 62 years	**Outcome expressed as % of days with correct number of doses taken , follow-up at 8 weeks (after crossover)** with enalapril once daily with enalapril twice daily	P <0.001	○○○	simplified dosing

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
then groups crossed over					
[40] RCT **3-armed trial**	405 people with chronic heart failure and left ventricular dysfunction The remaining arm evaluated carvedilol (controlled release formulation) taken in the morning and placebo taken in the afternoon	**Mean compliance measured by an electronic monitoring system (MEMS) , 5 months** 89% with carvedilol twice daily (immediate release formulation) 88% with carvedilol once daily (controlled release formulation) Absolute numbers not reported	Differential mean compliance was +1.1% 95% CI –4.4% to +6.6% P = 0.62	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[36] RCT	7274 people with hypertension, suitable for treatment with nicardipine, age 18 years and older, mean age 50 years, 60% on current treatment. Other concomitant antihypertensive therapies allowed	**Pruritus** with nicardipine twice daily (slow release) with nicardipine 3 times daily Absolute results not reported	P = 0.043	○○○	simplified dosing
[36] RCT	7274 people with hypertension, suitable for treatment with nicardipine, age 18 years and older, mean age 50 years, 60% on current treatment. Other concomitant antihypertensive therapies allowed	**Palpitations** with nicardipine twice daily (slow release) with nicardipine 3 times daily Absolute results not reported	P = 0.033	○○○	simplified dosing
[36] RCT	7274 people with hypertension, suitable for treatment with nicardipine, age 18 years and older, mean age 50 years, 60% on current treatment. Other concomitant antihypertensive therapies allowed	**People with at least 1 adverse event** with nicardipine twice daily (slow release) with nicardipine 3 times daily Absolute results not reported	P = 0.004	○○○	simplified dosing
[36] RCT	7274 people with hypertension, suitable for treatment with nicardipine, age 18 years and older, mean age 50 years, 60% on current treatment. Other concomitant	**Hot flushes** with nicardipine twice daily (slow release) with nicardipine 3 times daily Absolute results not reported	P = 0.024	○○○	simplified dosing

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	antihypertensive therapies allowed				
[37] RCT **Crossover design** Intervention continued for 8 months, then groups were crossed over for further 8 months	29 men, participants in earlier study, mean age 49 years, on niacin 4 times daily plus lovastatin twice daily plus colestipol twice daily for 1 year, adjusted to maintain target cholesterol 150 mg/dL to 175 mg/dL, high risk of cardiac events (elevated apoprotein B or stenosis or strong family history). Other medication (lovastatin and colestipol) continued as before	**Flushing** 14 people with niacin twice daily 6 people with niacin 4 times daily Absolute numbers not reported	P <0.005	○○○	complex dosing

No data from the following reference on this outcome. [35] [38] [39] [40]

Simplified dosing versus patient health education, prompting mechanisms, prescriber education, or reminder packaging:

We found 10 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] 2003; [21] [33] [34] 2004; [23] 2007; [24] 2008 [25]), which identified no RCTs of sufficient quality. The reviews did not pool data. We found no subsequent RCTs.

Further information on studies

[35] Method of randomisation not described. Level of blinding not reported. Loss to follow-up 50/389 (13%). No significant difference between groups in blood pressure control measured in clinic (P value not reported). Subgroup also participated in home blood pressure monitoring; these results not presented here. The RCT found no significant difference in adverse effects between once-daily and twice-daily metoprolol.

[36] Method of randomisation was described. Open RCT. Results based on 6813/7274 (94%) of those randomised. The treating physicians' estimates of participants' compliance were consistent with the participants' estimates. Adherence measured by self-reporting. Acceptability of twice-daily treatment was rated significantly higher by participants compared with three-times-daily (P <0.001). No significant difference between groups in blood pressure control (P = 0.185).

[37] Method of randomisation not described. Level of blinding not reported. Crossover RCT — results should be interpreted with caution.

[38] Method of randomisation not described. Participants were aware that cap was recording opening of bottle. Follow-up 29/31 (94%). Small RCT. No significant differences between groups in number of angina attacks or mean number of rescue GTN tablets taken (P value not reported). The RCT reported that none of the differences in tolerability were significantly different between once- and twice-daily isosorbide mononitrate (absolute numbers and P value not reported).

[39] Randomisation method not described. Evaluation blinded. Follow-up 25/27 (93%). All groups received home visits every 2 weeks for duration of study. Third 4-week treatment period incorporated into study design to detect carryover effects, as no wash-out period between treatments. Crossover RCT — results should be interpreted

with caution. No significant difference between groups in blood pressure measurements, although differences approached significance in favour of the twice-daily regimen.

[40] The three-arm randomisation format of this trial was designed to evaluate the effect of a twice-daily versus once-daily formulation of carvedilol in a double-blinded manner as well as to evaluate the two dosing regimens in a real-world effectiveness format (twice-daily carvedilol IR compared with the open-label arm of once-daily controlled release carvedilol CR). Randomisation method not described. Follow-up 401/405 (99%). There were also no significant differences in quality of life, treatment satisfaction, or physiological measures among the study arms. This review only analyses the treatment arms of immediate release versus controlled release, as these are the comparisons relevant for assessing adherence.

Comment:

In this option we have included any RCTs that compared any form of simplified dosing (i.e., a reduction in the number of tablets taken daily). All included RCTs compared different regimens of the same drug. We excluded RCTs that compared different drugs in each arm (e.g., one drug once daily *v* a different drug twice daily), as the different drugs in each arm may have different acceptabilities, which may affect adherence in each arm, making interpretation of adherence between groups difficult.

Fixed-dose combinations: We found one systematic review (search date 2008, 15 studies [5 RCTs, 4 CCTs, 6 retrospective cohort studies], 32,331 people), [41] which was a meta-analysis of the compliance, safety, and effectiveness of fixed-dose combinations (FDCs) of antihypertensive agents. The review did not present results separately from RCTs for our outcome of interest (adherence). It found that the use of FDCs significantly improved compliance compared with individual drugs given as separate tablets. It found no significant difference in persistence with therapy, systolic or diastolic blood pressure, or adverse effects between groups.

Clinical guide:

The relatively limited evidence (1 meta-analysis, small number of RCTs and short follow-up period) supports the strategy of simplifying the dosage of medication when prescribing cardiovascular medicines. Whether simplification of dosage influences adherence when a patient is taking multiple drugs (the usual situation in secondary prevention of CHD) is not known. Similarly, the trade-off between simplification of dosage to enhance adherence balanced against the risk of altered pharmacodynamics and pharmacokinetics, particularly in older patients at risk of adverse drug reactions, is also unknown. Nevertheless, provision of simple, clear instructions alongside simplification of the dosage regimen seems a sensible and pragmatic strategy. [1]

OPTION PRESCRIBER EDUCATION

- For GRADE evaluation of interventions for Cardiovascular medication: improving adherence, see table, p 31 .
- We found one RCT of prescriber education in a developing country which showed that a 1-day intensive training session of general practitioners on hypertension improved medication adherence compared with usual care but these data are not generalisable to the range of people taking cardiovascular medication so we cannot draw firm conclusions about this intervention.

Benefits and harms

Prescriber education versus usual care:

We found 8 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] 2003; [21] 2004; [23] 2007; [24] 2008 [25]), which identified one RCT of sufficient quality. [43] We found no subsequent RCTs.

Adherence to medication

Compared with usual care Prescriber education may be more effective than usual care at improving adherence in people in developing countries who are taking antihypertensive medication (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prescriber education					
[43] RCT	200 people with hypertension and taking antihypertensive medications	**Percentage of days on which correct dose of medication was taken, measured by an electronic measuring system (MEMS) , 6 weeks**	P = 0.048	○○○	prescriber education

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(see further information on studies)	48% with prescriber education 32% with usual care Absolute numbers not reported			

Adverse effects

No data from the following reference on this outcome. [43]

Prescriber education versus prompting mechanisms, patient health education, simplified dosing, or reminder packaging:

We found 8 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] 2003; [21] 2004; [23] 2007; [24] 2008 [25]), which found no RCTs of sufficient quality. We found no subsequent RCTs.

Further information on studies

[43] This cluster randomised controlled trial sought to determine the impact of a simple educational package for general practitioners on adherence to antihypertensive drugs in a developing world setting. Six randomly selected communities in Karachi, Pakistan, from which 200 people with hypertension taking antihypertensive drugs and being treated by 78 general practitioners, were randomised. Method of randomisation was described as a multi-stage cluster random sampling technique using computer-generated codes. **Intervention** The intervention was a 1-day intensive training session on hypertension, which focused on standard treatment algorithms for the management of hypertension. Of the 200 people who were enrolled, 178 (89%) successfully completed 6 weeks of follow-up.

Comment: In this option, "prescriber education" refers to a prescribing clinician who has received a directed intervention (educational) aimed at improving medication adherence in people to whom he or she has prescribed; this is compared with adherence achieved by another clinician of a similar overall training level, but who has not received the educational intervention.

Clinical guide:
Prescribers play a key initial role in the process of adherence to medication within the setting of a therapeutic alliance between clinician and patient. However, they still remain removed from the process of medication-taking, which is the ultimate determinant of adherence. Despite this, educational interventions can be directed at prescribers with the aim of improving adherence, but studies of sufficient methodological rigour have yet to be carried out.

OPTION REMINDER PACKAGING (CALENDAR [BLISTER] PACKS; MULTI-DOSE PILL BOXES)

- For GRADE evaluation of interventions for Cardiovascular medication: improving adherence, see table, p 31 .
- We found no evidence from one RCT that reminder packaging (a calendar blister pack) was effective, and found insufficient evidence on other types of reminder packaging such as multi-dose pill boxes. Reminder packaging using a calendar blister pack seems effective, but we don't know whether other types of reminder packaging, such as multi-dose pill boxes, improve adherence.

Benefits and harms

Calendar (blister) pack versus usual care:

We found 11 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] 2003; [21] [34] 2004; [23] [44] 2007; [24] 2008; [25] 2009 [26]), which identified two RCTs of sufficient quality. [45] [46]

Adherence to medication

Compared with usual care We don't know whether packaging medication in calendar (blister) packs is more effective than packaging medication in traditional (usual) vials at improving adherence to medication in people with hypertension (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to medication					
[45] RCT	180 people aged 20 to 80 years with elevated diastolic blood pressure >90 mmHg on at least 1 visit in the 2 years prior to the study; recruited from people receiving care at a community hospital-based family medicine practice	**People taking >80% of pills (self-reported) , at 3 months** 56% with special packaging 54% with traditional (usual) pill vials Absolute numbers not reported The special packaging was a commercially available system comprising 28 doses of medication. Each pill was enclosed in a single plastic blister sealed with foil, on which was printed the day of week and time of day the medication was due	Reported as not significant P value not reported	⟷	Not significant
[45] RCT	180 people aged 20 to 80 years with elevated diastolic blood pressure >90 mmHg on at least 1 visit in the 2 years prior to the study; recruited from people receiving care at a community hospital-based family medicine practice	**People taking >80% of pills (measured by pill count) , at 3 months** 84% with special packaging 75% with traditional (usual) pill vials Absolute numbers not reported 158/180 (88%) of people analysed The special packaging was a commercially available system comprising 28 doses of medication. Each pill was enclosed in a single plastic blister sealed with foil, on which was printed the day of week and time of day the medication was due	Reported as not significant P value not reported	⟷	Not significant
[46] RCT	85 people 65 years of age or older with hypertension in the US	**Prescription refill regularity , 12 months** 80% with daily dose blister packaging 66% with traditional pill bottles Absolute numbers not reported	P = 0.012	○○○	daily dose blister packaging
[46] RCT	85 people 65 years of age or older with hypertension in the US	**Medication possession ratio , 12 months** 0.93 with daily dose blister packaging 0.87 with traditional pill bottles Absolute numbers not reported	P = 0.039	○○○	daily dose blister packaging

Adverse effects

No data from the following reference on this outcome. [45] [46]

Calendar (blister) packs versus simplified dosing, patient health education, prompting mechanisms, prescriber education, or multi-dose pill boxes:

We found 12 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] 2003; [21] [34] 2004; [23] [44] 2007; [24] 2008; [25] [46] 2009 [26]), which identified no RCTs of sufficient quality.

Multi-dose pill box (unit-of-use packaging) plus usual care versus usual care alone versus prompting mechanism plus usual care versus multi-dose pill box (unit-of-use packaging) plus prompting mechanism plus usual care:

See option on prompting mechanisms, p 4 .

Multi-dose pill boxes versus calendar (blister) packs, simplified dosing, patient health education, or prescriber education:

We found 12 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] 2003; [21] [34] 2004; [23] [44] 2007; [24] 2008; [25] [46] 2009 [26]), which identified no RCTs of sufficient quality.

Further information on studies

[45] The RCT also found no significant difference between groups in average diastolic blood pressures at 3 months (165 people assessed). Method of randomisation not described. Physicians treating people were blinded to the study group; it was not reported whether assessment was blinded. Loss to follow-up at first follow-up visit was 15/180 (8%). In contrast to previously reported work, this RCT did not demonstrate any significant improvement in compliance with special packaging of antihypertensive medications.

[46] The RCT found that patients using daily-dose blister packaging had lower diastolic blood pressure (P = 0.01) than patients who had their medications packaged in traditional bottles of loose tablets. **Open study** Method of randomisation was described as randomisation logs provided by the university department of biostatistics. No losses to follow-up reported.

Comment:

In addition to the studies above, we found one open-label crossover RCT (784 people in Poland with uncontrolled hypertension), which assessed the impact of an electronic reminder and monitoring device compared with usual care over 12 months. [47] It found a significant difference in adherence in favour of the device between groups at 6 months, but this difference diminished after crossover. Adherence was assessed by use of a self-reporting questionnaire. Blood pressure was not affected. Method of randomisation was not described. Losses to follow-up were substantial, at 50% (386/784), and for this reason this study did not meet *Clinical Evidence* reporting inclusion criteria.

Clinical guide:

Reminder packaging now appears commonly in clinical practice as more and more drug companies produce their medications in calendar packs, and the use of multi-dose pill boxes, especially for older people, continues to rise. Although the benefit seems self-evident, there are few data published on the subject. The only RCT of sufficient quality included here on calendar (blister) packs, which compared medications dispensed in special packaging versus medications dispensed in traditional pill vials, [45] found no significant difference between groups in adherence.

OPTION PATIENT HEALTH EDUCATION

- For GRADE evaluation of interventions for Cardiovascular medication: improving adherence, see table, p 31 .
- Patient health education may also increase adherence to medication.
- Adherence behaviour is complex. Traditional education methods may fail to address this. However, more patient-centred approaches, particularly those that are nurse- or pharmacist-led, using video or telephone strategies, may be beneficial and require further investigation.
- We found some RCT evidence that a combination of strategies, such as education plus prompting, may be more successful than a single educational strategy.

Benefits and harms

Patient health education versus usual care:

We found 10 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] 2003; [21] [33] 2004; [23] 2007; [24] 2008; [25] 2009 [26]), which between them identified 12 RCTs (34–2618 people) [48] [49] [50] [51] [52] [53] [54] [55] [56] [57] [58] [59] including one extended follow-up report of one RCT, [60] and we found one additional RCT. [61] The RCTs employed a number of educational interventions and assessed different measures of adherence; for full details on interventions, see further information on studies. Some of the RCTs were of poor methodological quality, and completeness of reporting varied widely between trials.

Adherence to medication

Compared with usual care Patient health education may be no more effective than usual care at improving adherence in people taking cardiovascular medication. However, the education interventions used were diverse, and results varied by the specific educational intervention employed (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to medication					
[48] RCT	230 male steelworkers, with hypertension, not on current treatment. Of 115 in each group, 80 (70%) in education group and 64 (56%) in no education group received drug treatment. These 144 men were analysed	**Assessment by pill count (compliance defined as the % of medication prescribed that was removed from the bottle; defined as "compliant" if compliance pill count of 80% or more) , 6 months follow-up** 40/80 (50%) with educational intervention 36/64 (56%) with no health education	Similar rates of adherence between groups, but differences not tested statistically		
[49] RCT Some reported data from systematic review as well as original report of RCT	110 people, mean age 56 years, started on lipid-lowering medication (fluvastatin) mainly for primary prevention	**Outcome (% of pills taken assessed by pill count) , follow-up at 4 months** 88% with educational intervention 84% with usual care Absolute numbers not reported	P >0.05	⟷	Not significant
[50] RCT Some reported data from systematic review as well as original report of RCT	110 people, with either newly diagnosed or established treated hypertension, mean age 59 years	**Adherence assessed by pill count , 6 months follow-up** 93% with educational intervention 69% with usual care Absolute numbers not reported	P <0.002	○○○	educational intervention

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[60] RCT RCT [60] is a 2-year follow-up report of previous RCT [50] Some reported data from systematic review [18] as well as original report of RCT	110 people, with either newly diagnosed or established treated hypertension, mean age 59 years	**Adherence assessed by pill count , 2 years' follow-up** 96% with educational intervention 56% with usual care Absolute numbers not reported	P <0.001	○○○	educational intervention
[51] RCT **4-armed trial**	115 people attending a primary care clinic, <70 years old, with hypertension, living near to clinic	**Self-reported compliance (survey conducted by nurse, household medicated survey, which included questions on drugs and a count of all hypertensive medications; outcome reported as absolute numbers of "good", "fair", and "poor" compliance)** 8 people reported as "good", 13 "fair", 8 "poor" with educational intervention 7, 13, 5 people with daily self-monitoring of blood pressure 9, 15, 6 people with education and self-monitoring of blood pressure 7, 12, 10 people with control	RCT reported "no significant difference between groups on compliance"	⟷	Not significant
[52] RCT **3-armed trial**	417 people with hypertension, on medication RCT had 2 different educational groups versus control. Results for both educational groups combined in analysis	**Self-reported compliance at interview** 91% with educational intervention 90% with no education Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[52] RCT **3-armed trial**	417 people with hypertension, on medication RCT had 2 different educational groups versus control. Results for both educational groups combined in analysis	**Analysis of number of tablets prescribed by pharmacy records** 69% with educational intervention 68% with no education Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[53] RCT	34 people with hypertension on treatment, age 16 years or older (average age 51–56 years), at tertiary care medical centre	**Self-reported compliance as assessed by interview with questionnaire (score measured on 6-point scale, where 0 = no adherence and 5 = all tablets taken) (possible total score of 30) , 6 months** 27.53 with educational intervention 24.46 with usual care	P = 0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[53] RCT	34 people with hypertension on treatment, age 16 years or older (average age 51–56 years), at tertiary care medical centre	**Physician's assessment of adherence (score measured on 6-point scale, where 0 = no adherence and 5 = all tablets taken) (possible total score of 30) , 6 months** 29.18 with educational intervention 23.9 with usual care	P = 0.003 Not clear on what basis the physician's assessment of adherence was made	○○○	educational intervention
[54] RCT	Participants chosen from database by prescription (rather than diagnosis), 410 people taking benazepril, 1728 taking metoprolol, and 568 taking simvastatin, mean age 55 years (range 20–97 years), with refill of medication every 30 days Subgroup analysis This analysis is of 410 people taking benazepril	**Index of compliance was medication possession ratio (MPR), calculated from pharmacy records (MPR defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied) , over 9 months** 0.71 with educational intervention 0.72 with usual care	Reported as not significant P value not reported	⟷	Not significant
[54] RCT	Participants chosen from database by prescription (rather than diagnosis), 410 people taking benazepril, 1728 taking metoprolol, and 568 taking simvastatin, mean age 55 years (range 20–97 years), with refill of medication every 30 days Subgroup analysis This analysis is of 1728 people taking metoprolol	**Index of compliance was medication possession ratio (MPR), calculated from pharmacy records (MPR defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied) , over 9 months** 0.74 with educational intervention 0.73 with usual care	Reported as not significant P value not reported	⟷	Not significant
[54] RCT	Participants chosen from database by prescription (rather than diagnosis), 410 people taking benazepril, 1728 taking metoprolol, and 568 taking simvastatin, mean age 55 years (range 20–97 years), with refill of medication every 30 days Subgroup analysis This analysis is of 568 people taking simvastatin	**Index of compliance was medication possession ratio (MPR), calculated from pharmacy records (MPR defined as the number of days' supply of medication obtained throughout the study period expressed as a ratio against the number of days that should have been supplied) , over 9 months** 0.73 with educational intervention 0.70 with usual care	Reported as not significant P value not reported	⟷	Not significant
[55] RCT	100 people >70 years of age with chronic stable	**Mean compliance, expressed as % of maximum number of tablets that should have been**	P <0.001	○○○	educational intervention

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	heart failure, average age age 85 years, excluded if mobility disorder or if Folstein's Mental Health test score was <21	**consumed (assessed by pill count)** 93% with educational intervention 51% with control Absolute numbers not reported			
[58] RCT	245 people with hypertension, on 1 or more medications, attending primary care	**Adherence measured by electronic medication monitor (electronic lid that registered time and date of opening); mean "timing compliance" defined as number of doses taken at 24- or 12-hour intervals for a once- or twice-daily regimen respectively, divided by the total number of days x 100% , 6 months** 87% with educational intervention 90% with usual care Absolute numbers not reported	Adjusted difference between means –1 95% CI –5.1 to +3.1 P = 0.63	⟷	Not significant
[61] RCT	314 people with heart failure, 50 years or older, attending primary care, on at least 1 medication Intervention lasted for 9 months	**Adherence measured by electronic medication monitor (electronic lid that registered time and date of opening); "taking adherence" was defined as the % of prescribed medication taken , over 9 months** 79% with educational intervention 68% with usual care Absolute numbers not reported	Difference +11% 95% CI +5.0% to +16.7%	○○○	educational intervention
[61] RCT	314 people with heart failure, 50 years or older, attending primary care, on at least 1 medication Intervention lasted for 9 months	**Adherence measured by electronic medication monitor (electronic lid that registered time and date of opening); "scheduling adherence" was defined as day-to-day deviation in timing of dose (e.g., once-daily within 2.4 hours of dose on previous day) , over 9 months** 53% with educational intervention 47% with usual care Absolute numbers not reported	Difference +6% 95% CI +0.4% to +11.5%	○○○	educational intervention
[61] RCT	314 people with heart failure, 50 years or older, attending primary care, on at least 1 medication Intervention lasted for 9 months	**Adherence measured by electronic medication monitor (electronic lid that registered time and date of opening); "taking adherence" was defined as the % of prescribed medication taken , 3 months after intervention had finished** 71% with educational intervention 67% with usual care Absolute numbers not reported	Difference +4% 95% CI –2.8% to +10.7%	⟷	Not significant
[61] RCT	314 people with heart failure, 50 years or older, attending primary care, on at least 1 medication	**Adherence measured by electronic medication monitor (electronic lid that registered time and date of opening); "scheduling adherence" was defined as day-to-day deviation**	Difference +0.3% 95% CI –5.9% to +6.5%	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Intervention lasted for 9 months	**in timing of dose (e.g., once-daily within 2.4 hours of dose on previous day) , 3 months after intervention had finished** 48.9% with educational intervention 48.6% with usual care Absolute numbers not reported			
[56] RCT	636 adults with hypertension, attending primary care, using hypertensive medication at the time of baseline visit	**Increase in self-rated adherence (assessed using the 4-item Morisky Self-reported Medication-Taking Scale), reported as a %** 9% with nurse-delivered educational/behavioural intervention by protocol, bi-monthly via telephone for 2 years 1% with usual care Absolute numbers not reported			
[59] RCT	190 African-Americans with hypertension (88% women; mean age 54 years), attending community-based primary care practices	**Adherence measured by electronic pill monitors , 12 months** 57% with research assistant (RA)-delivered motivational interviewing (MINT) sessions at 3, 6, 9, and 12 months 43% with usual care Absolute numbers not reported	Difference –14% 95% CI –0.2% to –27% P = 0.027	○○○	MINT
[57] RCT	450 people with hypertension attending primary care	**Overall compliance rate (individuals with a treatment compliance of 80–110%) , 24 weeks** 83% with educational magazine sent to the patient's home twice monthly 49% with usual care Absolute numbers not reported	P = 0.0001	○○○	educational magazine
[57] RCT	450 people with hypertension attending primary care	**Correct time compliers , 24 weeks** 74% with educational magazine sent to the patient's home twice monthly 42% with usual care Absolute numbers not reported	P = 0.0001	○○○	educational magazine

Adverse effects

No data from the following reference on this outcome. [48] [49] [50] [51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61]

Patient health education plus prompting mechanism versus usual care:

See option on prompting mechanisms, p 4 .

Patient health education versus prompting mechanisms, prescriber education, simplified dosing, or reminder packaging:

We found 10 systematic reviews (search dates 1996; [16] 2000; [17] 2002; [18] [19] 2003; [21] [33] 2004; [23] 2007; [24] 2008; [25] 2009 [26]), which identified no RCTs of sufficient quality.

Further information on studies

[48] **Educational intervention** Educational programme on facts about hypertension, benefits of treatment, need for compliance, slide–audiotape format and booklet, and "patient educator" (non-health professional) to reinforce messages. **RCT methods** Method of randomisation not described. Factorial design. Steelworkers also randomised to family doctor or industrial physician care at the same time to see if difference in outcome; these results not reported here. Interpretation complicated by factorial design, and only 144 (62%) of those randomised received drug treatment — results based on these 144 men.

[49] **Educational intervention** Small group training followed by postal information packages. **RCT methods** Final end points compared, not adjusted for baseline differences. **Clinical outcomes** RCT found no significant difference between groups for mean total cholesterol (P = 0.26), mean LDL (P = 0.48), or mean HDL (P = 0.48). [25] Educational intervention significantly reduced triglyceride compared with usual care (P <0.05). [25]

[50] [60] **Educational intervention** Group education (units of 15 people over 90 minutes, information about blood pressure management and importance of adherence) and additional postal education at 1, 3, and 5 months. **RCT methods** Method of randomisation not described; not reported if outcome assessment blinded; withdrawal 15/110 (14%) at 6 months and 18/110 (16%) at 2 years. [18]

[51] **Educational intervention** Four 90-minute meetings, emphasising importance of hypertension, including videotape and other standard material, and general health education. **RCT methods** Randomisation procedure was described. Compliance categorised as "good", "fair", or "poor", the basis of which not explained. Hence, difficult to interpret results.

[52] **Educational intervention** Either "Threatening message" group: print informational tabloid containing material on hypertension, its effects, control measures, and instructions on following regimen (this version emphasised severity of hypertension and consequences) or "Positive message" group: print tabloid as above, but emphasised positive health aspects of treatment. **RCT methods** Factorial design — people sequentially allocated to different interventions. Only the first randomisation reported here. Method of randomisation not described. Level of blinding not reported. At outset, 87% of participants were on medication. Follow-up for self-report scores and pharmacy scores unclear.

[53] **Educational intervention** A 30- to 40-minute intervention with nurse practitioner and follow-up telephone call 4 weeks later; included reinforcement of regimen, brochure, 12-minute audiovisual presentation, discussion of risk factors, and postcard reminder of next appointment. **RCT methods** Method of randomisation not described. Level of blinding not described. Small study. Differential withdrawals — results based on 17/17 (100%) in intervention group and 13/17 (76%) in control group.

[54] **Educational intervention** Single mailing of one relevant educational videotape on drug prescribed and inferred disease state, 30 minutes long, including advice on compliance. **RCT methods** People selected by medication from computerised database. RCT inferred that people taking benazepril and metoprolol had hypertension and those taking simvastatin had hyperlipidaemia, which may or may not be the case. Also investigated people with transdermal oestrogen; these results not reported here. Method of randomisation, level of blinding, and loss to follow-up not reported. Not known if all participants in videotape group had access to a video player.

[55] **Educational intervention** Counselling programme including a standard written protocol employing verbal counselling, medication calendars, and information leaflets. **RCT methods** Method of randomisation not described. Follow-up 82/100 (82%).

[58] **Educational intervention** Adherence support session with practice nurse (20 minutes) followed by reinforcement session (10 minutes), which explored patient concerns regarding medication, whether person understood diagnosis, and strategies to resolve medication problems. **RCT methods** Method of randomisation was described. Open label. Follow-up 204/245 (83%). Trial noted that it found higher levels of adherence to medication than in previous studies in similar populations. **Clinical outcomes** RCT found no significant difference between groups at 6 months with regard to systolic (P = 0.24) or diastolic (P = 0.85) blood pressure.

[61] **Educational intervention** Pharmacist-delivered intervention by protocol, including verbal and written material, exploring participant's understanding of disease or medication, and addressing low medication adherence. **RCT methods** Method of randomisation was described. Assessment blinded. Analysis based on 270/314 (86%) of those randomised. Found benefit when the intervention was being applied over the study period, which dissipated over 3 months after the intervention had finished.

[56] **Educational intervention** Nurse-led intervention delivered by telephone every 8 weeks over 6 months. Patient factors targeted in the tailored behavioural intervention include perceived risk of hypertension and knowledge, memory, medical and social support, patients' relationship with their health care provider, adverse effects of medication therapy, weight management, exercise, diet, stress, smoking, and alcohol use; Self-rated adherence was assessed using the 4-item Morisky Self-reported Medication-Taking Scale [Morisky 1986]. The scale for each item was revised to include the response categories "strongly agree", "agree", "disagree", and "strongly disagree". Those individuals who reported "strongly agree", "agree", "do not know", or "refused" to any of the 4 items were classified as non-adherent. Reported as a percentage and measured at baseline and post-intervention (6 months). **RCT methods** Method of randomisation not described. Follow-up reported as 96% retention rate at 6 months; otherwise not specified.

[59] **Educational intervention** Motivational interviewing. **RCT methods** Method of randomisation was described. After baseline assessment, patients were randomly assigned to either UC or MINT group by the study statistician, using sealed envelopes. Separate randomisation schedules were developed from a computerised random-number generator, balanced at set intervals, using permutated blocks, to assure equal numbers in each group. Owing to the nature of the behavioural intervention, neither the patients nor the RAs were blinded to the intervention. However, the clinic staff who recorded the blood pressure data were blinded to patient assignment. It is important to note that medication adherence data were downloaded automatically into the computer from the MEMS caps. Thus, neither the researchers nor the patients could affect MEMS adherence outcome. Results based on 83% (79/95) of intervention group and 85% (81/95) of UC group. **Clinical outcomes** Motivational interviewing over 12 months led to a steady maintenance of medication adherence, compared with significant decline in adherence for the usual care group. This effect was associated with a modest, non-significant trend towards a net reduction in systolic blood pressure in favour of intervention.

[57] **Educational intervention** Educational magazine sent to the patient's home twice monthly. **RCT methods** Method of randomisation was not described. Follow-up 393/450(87%). **Clinical outcomes** Educational magazine led to increased adherence and improved blood pressure control.

Comment:

Clinical guide:

Most factors known to affect adherence to medication — such as knowledge, health beliefs, perception of risk, convenience, and memory — relate to the patient. It is therefore not surprising that interventions to address adherence should focus on patient education, but what is perhaps surprising is that such interventions do not seem to have greater influence on adherence. However, the phenomenon of adherence is complex, and traditional educational methods may fail to recognise this. People's beliefs and preferences need to be acknowledged and incorporated into adherence-enhancing interventions. [62] A combination of strategies including prompting mechanisms and simplified dosing, alongside patient education with emphasis on the patient's perspective, may have a more successful impact on adherence. The rationale that the complexity of adherence behaviour may respond better to a multi-factorial approach that is patient-centred is supported by an RCT of an educational intervention plus a prompting intervention that significantly improved adherence compared with usual care, [32] by an RCT that used a combination of face-to-face education and follow-up postal education, [50] [60] by an RCT of a nurse-delivered telephone intervention that increased self-reported medication adherence by 9% in the intervention group versus 1% in the usual care group, [56] and by an RCT of motivational interviewing delivered every 3 months over 12 months, which led to a steady maintenance of medication adherence compared with significant decline in adherence for the usual care group. [59]

GLOSSARY

Fixed-dose combination A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Mini-Mental score A score derived from the Folstein Mini Mental State Examination. This examination is used to evaluate dementia, and consists of a series of questions and tasks to assess a patient's orientation, attention, calculation, language, visuospatial, executive, and short-term memory abilities. The cut off for dementia is a score of less than 24 out of a possible 30.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Prescriber education New evidence added. [24] [25] [43] Categorisation unchanged (Unknown effectiveness) because current evidence is in a single restricted population only.

Prompting mechanisms New evidence added. [24] [25] [26] Categorisation unchanged (Likely to be beneficial).

Reminder packaging (calendar [blister] packs; multi-dose pill boxes) New evidence added. [24] [25] [26] [46] Categorisation unchanged (Unknown effectiveness) because of conflicting results among trials.

Simplified dosing New evidence added. [24] [26] [40] [42] Categorisation unchanged (Likely to be beneficial).

Patient health education New evidence added. [24] [25] [26] [56] [57] [59] Categorisation changed from Unlikely to be beneficial to Unknown effectiveness because of conflicting results among trials; new evidence suggests that some more patient-centred approaches to education, using newer media, may be effective whereas traditional education fails to improve adherence.

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Disclaimer

TABLE 1 **Definitions of different types of reminder packaging***

		Definitions of different types of reminder packaging
Pill boxes	1	Monitored dosage system (MDS): medications are manually packed into blister/bubble trays under the supervision of a pharmacist and then cold- or heat-sealed with foil. Examples of these systems are the Nomad® and Manrex®. Patients using an MDS are provided with weekly or monthly blister packs
	2	Multi-compartment compliance aid (MCA) or dose administration aid: these are plastic trays or boxes that hold 7 days of a patient's medicine and are divided into days of the week. Each day of the week has a sliding lid, which covers compartments for different dosing times (usually 4 compartments for each day). They are commonly but not exclusively used for multiple medications. Examples of these are Dosett®, Medidos®, and the Mediset
Pre-packaged blister packs	1	Calendar blister: a blister package designed to aid a patient's memory by incorporating the day/time when each dose is to be taken into the package design
	2	Unit dose: the prescribed amount of each dosage in a package. This type of packaging can incorporate a reminder system
	3	Unit of use: the exact amount of a drug treatment prepackaged by the manufacturer or pharmacist in standardised amounts. This type of packaging can incorporate a reminder system

* Source: Heneghan CJ, Glasziou P, Perera R. Reminder packaging for improving adherence to self-administered long term medication. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004. Copyright Cochrane Collaboration, reproduced with permission.

GRADE **Evaluation of interventions for Cardiovascular medication: improving adherence.**

Important outcomes					Adherence to medication				
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions to improve adherence to long-term medication for CVD in adults?									
5 (1107) [7] [27] [28] [29] [30]	Adherence to medication	Prompting mechanisms versus usual care	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and weak methods (method of randomisation not described, level of blinding not reported). Directness points deducted for diverse interventions affecting generalisability, and diverse range of outcome assessment and analysis
2 (432) [31] [6]	Adherence to medication	Prompting mechanism plus usual care versus unit-of-use packaging plus usual care versus unit-of-use packaging plus prompting mechanism plus usual care versus usual care alone	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods (method of randomisation not described, level of blinding not reported). Directness point deducted for unclear intervention (unit-of-use intervention not fully defined)
1 (453) [32]	Adherence to medication	Prompting mechanism plus patient health education versus usual care	4	–1	0	–1	0	Low	Quality point deducted for weak methods (method of randomisation not described, level of blinding not reported). Directness point deducted for unclear validity of outcome assessment/single measure of adherence used
6 (8155) [35] [36] [37] [38] [39] [40]	Adherence to medication	Simplified dosing regimens versus more complex regimens	4	–2	0	–1	0	Very low	Quality points deducted for weak methods (method of randomisation not described, level of blinding not reported) and inclusion of 2 crossover RCTs. Directness point deducted for diverse range of outcome assessment and analysis
1 (200) [43]	Adherence to medication	Prescriber education versus usual care	4	–1	0	–1	0	Low	Quality point deducted for uncertainty about randomisation method. Directness point deducted for restricted population (limited to a developing country)
2 (265) [45] [46]	Adherence to medication	Calendar (blister) pack versus usual care	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting of results and for weak methods (method of randomisation not described, level of blinding for outcome assessment not reported). Consistency point deducted for conflicting results
13 (at least 5437) [48] [49] [50] [60] [51] [52] [53] [54] [55] [58] [61] [56] [57] [59]	Adherence to medication	Patient health education versus usual care	4	–2	–1	–2	0	Very low	Quality points deducted for incomplete reporting of results and weak methods (method of randomisation not described, level of blinding not reported). Consistency point deducted for conflicting results. Directness points deducted for diverse interventions affecting generalisability and diverse range of outcome assessment and analysis

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.