Abstract

Aims: To critically appraise and synthesise the best available evidence on the effectiveness of interventions suitable for delivery by nurses, designed to enhance cardiac patients' adherence to their prescribed medications.

Background: Cardiac medications have significant health benefits for patients with heart disease, but patients' adherence to prescribed medications remains suboptimal.

Design: A Systematic quantitative review of intervention effects.

Data Sources: We conducted systematic searches for English-language, peer-reviewed randomised controlled trial publications via Medline, EMBASE, CINAHL, the Cochrane Library, ProQuest, Web of Science and Google Scholar search engine from January 2004 to December 2014.

Review methods. According to pre-determined inclusion criteria and exclusion criteria, authors extracted the eligible studies using a predefined form. Of 1,962 identified articles; 22 met the study inclusion criteria and were assessed for risk of bias using the Cochrane Collaboration's tool; 13 studies were included in the review.

Results: Study findings were presented descriptively and not combined due to the heterogeneity of studies. The 13 included articles described interventions categorised as: 1) multifaceted, and 2) behavioural and educational, comprising: 2a) text message and mail message, 2b) telephone calls, 2c) motivational interviewing and 2d) nurse-led counselling and education.

Conclusions: Substantial heterogeneity limited the robustness of any conclusions, but this review indicated that motivational interviewing and text messaging appeared promising as means to enhance cardiac medication adherence. Further randomised controlled trials are warranted to strengthen the evidence, and future research should also include integration of multifaceted strategies to build on the beneficial outcomes indicated by this review.

Summary Statements

Why is this research or review needed?

- Non-adherence to cardiovascular medicines is associated with greater risk of hospitalisation and mortality.
- Various studies examine the effectiveness of medication adherence interventions, but the evidence is inconsistent and unclear.
- Nurses play a key role in educating and supporting patients with their medication, but evidence is lacking for effective nurse-delivered interventions to promote medication adherence for cardiac patients.

What are the key findings?

- Multifaceted interventions that target individual behaviour change appear to offer most promising methods to enhance adherence to cardiovascular medications.
- Current evidence indicates that the components for multifaceted interventions most likely to sustain adherence to cardiac medication-taking include motivational interviewing, education and phone or text messaging.

How should the findings be used to influence policy/ practice/research?

- Findings provide evidence to support clinicians' choice of interventions designed to enhance medication adherence among patients with cardiac disease delivered by nurses.
- More rigorous methods are required for future studies to test the effectiveness of nurse-led adherence interventions, taking into account study design, sampling, choice of effective and feasible adherence measures and longer term sustainability of outcomes.
- Policy-makers should consider the opportunities offered by nurse-led medication adherence interventions, to enhance the contribution of nurses and thereby optimise the benefits to patients of their prescribed medications.

Keywords: cardiovascular medication, adherence, cardiac disease, systematic review, text message, motivational interviewing, nursing, nurse-led intervention.

Introduction

Medication non-adherence is a complex problem that poses an enormous health and economic burden. It is more common among older age population and patients who need multiple medications for their chronic conditions (Menditto *et al*. 2015). It has been estimated that inadequate adherence to treatment among patients with chronic diseases affects up to 50% of patients (Lee *et al*. 2006, Wilke et al. 2011). Non-adherence is a multifactorial phenomenon, affected by socio-economic status, health systems, disease states, pharmacological therapies and patient beliefs (Sabaté 2003). Supporting long-term adherence to medicines is; therefore, an essential component of patient management which requires effective interventions to help achieve sustained medication-taking. This systematic review therefore aimed to identify effective interventions used by nurses to improve cardiac patients' adherence to cardiac medications.

Background

Cardiovascular disease (CVD) remains the leading cause of mortality among men and women and is responsible for one third of all deaths worldwide (World Health Organization 2004). In developing countries, coronary heart disease (CHD) accounts for more than 4.5 million deaths per annum (Okrainec *et al*. 2004). Similar to international trends, CVD is the single greatest cause of death in Australia, accounting for the deaths of 11,733 males and 9,780 females in 2011 (Australian Institute of Health Welfare 2014). Although CHD is incurable, disease progress can be significantly slowed by cardio-protective medicines and lifestyle changes. Cardio-protective medicines are the primary therapy for CHD, but adherence to these medications is suboptimal, resulting in insufficient control of disease symptoms, and increased risk of future cardiovascular events, rehospitalisation and mortality (Baroletti and

Dell'Orfano 2010). According to the World Health Organisation, adherence is defined as "The extent to which a person's behaviour (taking medications, following a recommended diet and/or executing life-style changes) corresponds with the agreed recommendations of a health care provider" (Sabaté 2003). Adherence is necessary to receive the full benefits of the cardiac medications. The protective effects of the medications increase with the longer patients are taking the medication which is necessary to receive the full benefits as long-term continuation of the medications (McKenzie et al. 2015). Medication non-adherence has been defined as "taking less than 80% of prescribed doses and can also include taking too many doses", and it is associated with an increased risk of poor health, adverse clinical events, and mortality (Nieuwlaat *et al*. 2014). It is estimated that up to 50% of patients with CHD in high income countries do not take their medications (Laba *et al*. 2013). Poor medication adherence has been linked to recurrent cardiac events and adverse patient outcomes (Nieuwlaat *et al*. 2014, Poluzzi *et al*. 2011). The prevalence of patients in the aging Australian population who are non-adherent to cardiovascular medications has been reported to range from 14% to 43%, posing a serious barrier to secondary prevention (McKenzie *et al*. 2015). Thus, long term medication adherence in Australia remains unsatisfactory, with the situation changing very slowly (Simons *et al*. 2011). Poor medication adherence rates undermine the translation of the benefits of well-established evidence-based cardiovascular medicines into practice, reducing the effectiveness of secondary prevention therapies (Haynes *et al*. 2005). It is crucial that adherence to cardiovascular medicines is optimised to improve disease symptoms and prevent the onset of further serious cardiac events (van Dalem *et al*. 2012). Many rigorous randomised controlled trials (RCTs) have examined the effectiveness of interventions to enhance medication adherence in patients with CHD. A number of diverse and complex behavioural, educational, and combined intervention approaches and outcomes measures have emerged; however, the effectiveness of these interventions needs to be

carefully evaluated due to the diverse methodologies used in the studies. It is important that healthcare professionals are aware of effective practical strategies and have the necessary skills to translate these interventions to outpatient healthcare settings. The purpose of this systematic review was to identify and synthesise the best available evidence on the effectiveness of interventions within the nursing scope of practice, designed to enhance cardiac patients' adherence to cardio-protective medications.

The review

Aims

This review aimed to answer the following question: What is the best available evidence on effectiveness of interventions, suitable for delivery by nurses, designed to enhance cardiac patients' adherence to their prescribed cardio-protective medications?

Design

A systematic quantitative review of intervention effects was conducted according to the principles and processes of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2008). The guidelines produced by the NHS Centre for Reviews and Dissemination (Khan *et al*. 2001) was also followed. The PRISMA statement (Moher *et al*. 2009) was used to guide reporting of the review.

Search methods

A systematic literature search was conducted using six electronic databases: Medline, EMBASE, CINAHL, the Cochrane Library, ProQuest, and Web of Science. These databases and Google Scholar were searched for articles published in English between January 2004

and December 2014. The reference lists of all selected articles including review articles were searched for additional studies. The keywords used in the search strategy were based on the 'PICOS' framework to help find literature relevant to the research question (Table 1).

Studies were included if they reported the results of un-confounded evaluation of interventions that were suitable for delivery by nurses to increase medication adherence for patients with CHD. The following inclusion criteria were applied:

1) Study design was a RCT, clinical trial, or controlled clinical trial that examined the effectiveness of an intervention to increase adherence to medications among patient with cardiac disease, used for secondary prevention or treatment of cardiac disease in which an intervention group was compared to a control group who received standard care or a clearly justified comparison group;

2) The population of interest comprised male and female adults (>18 years old) with a diagnosis of a cardiac disease;

3) The intervention strategy was suitable (within the scope of practice) for delivery by nurses and had either a primary or secondary aim to increase the adherence to medication of patient with cardiac disease;

4) Patients were followed for at least 6 months;

5) Medication was self-administered, that is, was not administered by a health care professional or carer, and measured by any method e.g.: pill count, electronic monitoring, refill or prescription records, or self-reported data.

Studies were excluded if they targeted patients with heart valve disease or post-cardiac surgeries; were written in a language other than English; included non-cardiac disease patients; tested interventions that required delivery by a non-nursing healthcare professional, e.g. pharmacist; were conducted in inpatient settings; recruited patients aged < 18 years; contained no medication adherence measures; were non-trial-design-studies or had less than six months follow-up, because cardiovascular medications typically require long-term adherence.

Search outcome

In total, search strategies identified 1,962 citations of potential relevance. Initial screening of study titles and abstracts revealed that more than 95% of the retrieved studies did not meet the review inclusion criteria, leaving 92 papers for further evaluation. The full texts of these articles were then reviewed for relevance, resulting in the retention of 22 articles for assessment. Two further RCT publications were added from references lists of included articles. The flow of studies through the selection process is summarised in Figure 1.

Quality appraisal

The quality of the included studies was appraised independently by three authors (AA, PL & GL)using the Cochrane Collaboration's tool for assessing the risk of bias (Higgins and Green 2008) and discrepancies were resolved by discussion. The results are summarised in the Supplementary online table. After applying the Cochrane Collaboration's tool, 11 articles were excluded (Figure 1) due to high or unclear risk of bias (e.g. Selection bias, Randomisation bias). Details of excluded studies are available in the Electronic Supplementary Material, Appendix 1.

Data abstraction

Data were extracted and analysed by three authors using a predefined form. After quality appraisal of these articles, 13 were retained for the review. Details of data extracted are available in the supplementary online Table S2.

Synthesis

Multiple sources of heterogeneity (interventions, adherence measures, and outcomes) were observed across the included studies, and this meant that undertaking a formal meta-analysis was not appropriate. The heterogeneity was explored qualitatively by comparing the characteristics of included studies. Studies were grouped according to the main components of the interventions (see the supplementary online Table S3).

Results

These thirteen included studies contained data on 3,542 patients with cardiac disease. One study only included patients with myocardial infarction (Smith *et al*. 2008), and another targeted cardiac patients taking lipid-lowering medication (Nieuwkerk *et al*. 2012). Two studies included patients who were diagnosed with CHD (Jiang *et al*. 2007, Kripalani *et al*. 2012), and patients with Acute Coronary Syndrome (ACS) were included in two studies (Ho *et al*. 2014, Rinfret *et al*. 2013). The remaining seven studies recruited patients with hypertension (Beune *et al*. 2014, Hacihasanoğlu and Goözuöm 2011, Leiva *et al*. 2014, Ma *et al*. 2014, Ogedegbe *et al*. 2008, Schroeder *et al*. 2005, Wald *et al*. 2014). Four studies were conducted in the United States (Ho *et al*. 2014, Kripalani *et al*. 2012, Ogedegbe *et al*. 2008, Smith *et al*. 2008), two each were conducted in the United Kingdom (Schroeder *et al*. 2005, Wald *et al*. 2014), Netherlands (Beune *et al*. 2014, Nieuwkerk *et al*. 2012), and China (Jiang *et al*. 2007, Ma *et al*. 2014); one study was conducted in Canada (Rinfret *et al*. 2013), one in Spain (Leiva *et al*. 2014) and one in Turkey (Hacihasanoğlu and Goözuöm 2011). Seven of

the included trials took place in primary care practice clinics (Beune *et al*. 2014, Hacihasanoğlu and Goözuöm 2011, Jiang *et al*. 2007, Kripalani *et al*. 2012, Leiva *et al*. 2014, Ogedegbe *et al*. 2008, Wald *et al*. 2014), three in outpatient clinics (Nieuwkerk *et al*. 2012, Schroeder *et al*. 2005, Smith *et al*. 2008), two in community health centres (Ma *et al*. 2014, Rinfret *et al*. 2013), and one in Department of Veterans Affairs (VA) medical centres (Ho *et al*. 2014).

Participants were followed up for a minimum of six months. The median follow-up time was one year, ranging from six months to 24 months. Most studies achieved their endpoint outcomes at three to nine months. Interventions varied, with single, combined, and multifaceted component parts. Characteristics of the included studies are presented in **Table S3**.

Medication adherence measurement

Methods for measuring and monitoring medication regimen adherence varied in these trials. Adherence was measured by self-report in five studies (Beune *et al*. 2014, Hacihasanoğlu and Goözuöm 2011, Jiang *et al*. 2007, Ma *et al*. 2014, Nieuwkerk *et al*. 2012) and by pharmacy refill electronic data in five studies (Ho *et al*. 2014, Leiva *et al*. 2014, Rinfret *et al*. 2013, Smith *et al*. 2008, Wald *et al*. 2014). The Medication Event Monitoring System (MEMS) pill bottle caps was used in one study (Schroeder *et al*. 2005), and two studies applied a mix of two medication measurements by using self-report and MEMS (Kripalani *et al*. 2012, Ogedegbe *et al*. 2008).

Types of intervention

Characteristics of the interventions are presented in Table 4. Interventions were categorised according to their most prominent components and included: 1) Multifaceted and 2) Behavioural and educational interventions. The later comprised: 2a) Text message and mail

message, 2b) Telephone call, 2c) Motivational Interviewing, and 2d) Nurse-Led Counselling and Education. The complex nature of some interventions made them difficult to categorise, but this was done based on the main component of intervention. Three studies examined text message (TM) and/or mail message interventions (Kripalani *et al*. 2012, Smith *et al*. 2008, Wald *et al*. 2014); two studies tested multifaceted intervention strategies (Ho *et al*. 2014, Leiva *et al*. 2014); two studies investigated the effect of structured telephone calls (Hacihasanoğlu and Goözuöm 2011, Rinfret *et al*. 2013); and two studies utilized the motivational interviewing approach (Ma *et al*. 2014, Ogedegbe *et al*. 2008). Four interventions were classified as Nurse-Led Counselling and Education (Beune *et al*. 2014, Jiang *et al*. 2007, Nieuwkerk *et al*. 2012, Schroeder *et al*. 2005). The heterogeneity of measurement tools and methods precluded meta-analysis of baseline and post-intervention rates of adherence for the reviewed studies.

Multifaceted interventions

The effectiveness of multifaceted interventions for enhancing medication adherence was described and evaluated by two studies. Ho *et al*. (2014) utilised a four stage multifaceted intervention that entailed: medication reconciliation and tailoring, education about medications, collaborative care, and two types of scheduled voice messaging (educational and medication refill reminder calls). Similarly, Leiva *et al*. (2014) evaluated a multifaceted intervention incorporating motivational interviewing, pillbox reminders, family support, BP measurements and antihypertensive (AHT) reminder forms, and simplification of dosing regimens in patients with hypertension. Ho *et al*. (2014) found that adherence rate improved at 12 months follow-up by 89.3% in the intervention arm compared with 73.9% with usual care for four classes of medications. On the other hand, Leiva *et al*. (2014) found no significant between groups differences in antihypertensive adherence at 12 months (51.4%

vs. 50.8%) in intervention and control groups, respectively **(Table S3)**. The Ho *et al*. (2014) study was high quality; however, Leiva *et al*. (2014) did not employ a blinding process and delivery of the intervention by nurses varied according to their characteristics and the methods of delivery, possibly resulting in overestimation of the intervention effect **(Tables S3).** Overall, this type of intervention approach appeared likely to increase adherence to medications after hospital discharge post ACS and was costed at $360 per patient per year (Ho *et al*. 2014).

Text and mail message interventions

Three studies assessed the effectiveness of text message (Wald *et al*. 2014) and mail message reminders Kripalani *et al*. (2012), (Smith *et al*. 2008) to increase medication adherence among cardiac patients. In the Wald *et al*. (2014) study, participants in the intervention group received automatically generated daily TM reminders which questioned patients whether they had taken their blood pressure and/or lipid lowering medications; whether the message had reminded them to take it; if they had forgotten or whether they had simply not taken it**.** This study showed 16% improvement in medication adherence (95% CI 7%–24%, p< 0.001) at 6 months follow-up, and a statistically significant difference between groups of patients who had stopped medication completely and for those who continued to take <80% of the prescribed regimen **(Table S3)**. However, participants' high adherence rates at baseline and unclear randomisation and blinding procedures may have resulted in overestimation of the outcomes **(Tables S2).**

Another two studies applied a less individual approach, one by mailing graphical postcards focusing on refill reminding and other important reminders to patients with CHD (Kripalani *et al*. 2012), and another study focused on improving cognitive aspects of medication adherence by sending two letters to patients and to primary care providers describing the

importance of beta-blockade (Smith *et al*. 2008)**.** Kripalani *et al*. (2012) study showed a non-significant difference in improvements in adherence between groups (32.9% vs. 32.9% respectively) whereas the Smith *et al*. (2008) study improved adherence rates among patients in the intervention group by 17%, increasing the days covered to 80% in this group (relative risk= 1.17; 95% CI= 1.02-1.29; p= 0.04). The quality of Smith *et al*. (2008) study was shown as good in terms of randomisation methods, intervention and strategies used for applying the intervention and follow-up. By contrast, graphical mailed refill reminders failed to improve medication adherence, which was potentially attributed to quality issues, with randomisation and blinding processes **(Table S2)**. Overall, the TM and mail message approaches appeared potentially effective and feasible strategies as reinforcement for taking medication and improving medication adherence.

Telephone call interventions

Two studies (Hacihasanoğlu and Goözuöm 2011, Rinfret *et al*. 2013) examined the use of structured phone calls with interactive components to improve medication adherence. Hacihasanoğlu and Goözuöm (2011) randomly allocated patients with hypertension to three groups to receive a 6-month nurse-based medication educational intervention alone, educational intervention plus home monitoring for medication adherence, or a control group. Both intervention groups received monthly follow-up phone call interviews providing them with information about hypertension. Similarly, in the Rinfret *et al*. (2013) study, patients with dual antiplatelet therapy (DAT) (n=150) were randomised to either nurse phone calls within one week and then at one month, six months and nine months to assess adherence, reinforce optional drug compliance and discuss the factors affecting adherence or to a control group **(Table S3).** Both studies showed a significant increase in medication adherence using different measures. At 10 months follow up, there was a significant increase in regular

medication intake ratios after education in groups A and B (80%, 85%, respectively, p= 0.001) but not in the control group (42%, p> 0.05) (Hacihasanoğlu and Goözuöm 2011). Combined education (group B) was shown to have a more positive effect on adherence self-efficacy than education alone (group A) and no intervention (control group) 72.27 (SD= 5.27); 71.10 (SD= 6.42); 56.85 (SD= 6.10) respectively, F= 83.131; p= 0.001) (Hacihasanoğlu and Goözuöm 2011). The Rinfret *et al*. (2013) study showed that participants in both groups had high adherence to antiplatelet drugs at 12 months, with 99.2% (ranging from 97.5% to 100%) of the intervention group taking aspirin compared to 90.2% (ranging from 84.2% to 95.4%) of the control group; clopidogrel, 99.3% (ranging from 97.5% to 100%) in the intervention group vs. 91.5% (85.1-96.0%) % in the control group, (p< 0.0001). However, the study results may have been biased by the lack of blinding of patients and intervention providers, although it was impractical in this study **(Table S2).**

Theory-based structured phone calls were shown to have a significant impact on adherence and clinical outcomes. The success of the study by (Hacihasanoğlu and Goözuöm 2011) in reinforcing medication adherence of patients with hypertension by nurse phone calls indicates potential to increase the educational and counselling role of nurses in primary care.

Motivational interviewing strategies

Motivational interviewing has been used as an approach to increase adherence to medication in cardiac patients. Ogedegbe *et al*. (2008) conducted a randomised controlled trial in two community-based primary care practices in the US, evaluating the efficacy and effects of practice-based motivational interview (MINT) counselling on medication adherence and blood pressure (BP) in 190 African American patients with hypertension. Based on intention-to-treat analysis using mixed-effects regression, the MINT group achieved a higher MEMS adherence rate at 12 months follow-up compared to the control group (57% vs. 43%

respectively, $p < 0.05$), with an absolute between-group difference of 14% (95% CI, −0.2 to –27%). The MINT group received behavioural counselling about medication adherence for 30–40 minutes at three, six, nine, and 12 months, which led to steady maintenance of medication adherence over 12 months, while adherence rates declined overtime in the control group. Similarly, Ma *et al*. (2014) applied MINT counselling, based on social cognitive theory, to 120 patients with hypertension from two community health centres in China. This intervention entailed strategies to promote adherence to behaviour changes, summarising the pros and cons of proposed behaviour changes, setting realistic and specific goals for behaviour modification and prompting patients to follow plans for behaviour change (Table 3). Adherence to medication was improved in the MINT counselling group compared to the control group at six months follow-up 29.72 (SD= 3.46) vs. 25.30 (SD= 3.11) respectively, (t=0.039, p=0.034). Mean scores for medication adherence were increased within-groups with mean difference between baseline and six months for intervention group of 23.25 (SD= 3.02); 29.72 (SD= 3.46) respectively, (t= 0. 039, P= 0.034) and 22.13 (SD= 2.89); 25.30 (SD= 3.11) (t= 0. 039, P= 0.061) **(Table S3).** This form of MINT was theory-based, and shown to be effective using accepted valid measures for adherence assessment over longer duration of follow-up.

Nurse-led counselling and education

Four studies intended to improve medication adherence by using behavioural interventions and education through nurse-led counselling. Three studies demonstrated no or little evidence of effect (Beune *et al*. 2014, Jiang *et al*. 2007, Schroeder *et al*. 2005). These results may be attributed in part at least to feature of the research methods, such as self-selected populations with high adherence levels at baseline (Schroeder *et al*. 2005) and randomisation and blinding processes bias (Beune *et al*. 2014, Jiang *et al*. 2007) **(Table S2).** Nieuwkerk *et al*. (2012)

revealed that adherence to lipid lowering medication increased from 95% to100% in the intervention group and from 90% to 95% in the control group. At 18 months follow up, the intervention group had higher adherence to statin therapy than the control group 9.39 (SD= 0.15) vs 8.86 (SD= 0.15) respectively, with an absolute difference between groups of 0.53 (0.02-1.05), (r = -0.36, P< 0.01) **(Table S3).** With 201 patients on statin therapy randomised to receive nurse-led multifactorial cardio-vascular risk-factor counselling or standard care, significant outcomes were attributed to the more extensive personal contact with the nurse practitioner as well as risk-factor counselling in the intervention group compared to the control group. Overall, most studies demonstrated no improvement in outcomes from nurse-led behavioural interventions (Beune *et al*. 2014, Jiang *et al.* 2007, Schroeder *et al*. 2005), whilst Nieuwkerk *et al*. (2012) study appeared to offer an opportunity to improve medication adherence. However, taking into consideration the baseline difference between groups, results of this study should be interpreted with caution.

Risk of bias assessment

Risk of bias was assessed using the Cochrane Collaboration's tool (Higgins and Green 2008) based on the main sources of selection bias, performance bias, attrition bias, detection bias, reporting bias and systematic bias. These criteria were considered in the process of study assessment, as recommended by the Cochrane Handbook (Higgins and Green 2008). An overall assessment of the studies was performed by using the Cochrane quality assessment tool. All trials provided information about adequate sequence generation, 10 studies described the measures used to blind outcome assessors from knowledge of which intervention a participants received. However, performance bias was carefully avoided in four studies only (Beune *et al*. 2014, Jiang *et al*. 2007, Leiva *et al*. 2014, Ogedegbe *et al*.

2008) by providing information about adequate blinding of participants and personal. Nine studies reported the participants lost to follow up, and six trials only provided prior study protocol and reported the methods of examining the selective outcomes (medication adherence). The remaining studies did not provided a study protocol although they were reported all outcomes (Jiang *et al.* 2007, Kripalani *et al*. 2012, Leiva *et al*. 2014, Ogedegbe *et al*. 2008, Rinfret *et al*. 2013, Schroeder *et al*. 2005, Smith *et al*. 2008) (see Figure 2). In addition, the application of GRADE was used for grading the certainty of evidence of the findings, medication adherence. The grading scores was described as (-1 or +1) and summed to output an overall scores (4 = high, 3 = moderate, 2 = low and 1 = very low) based on the risk of bias, design, inconsistency, indirectness and imprecision where scores (EPOC Resources for review authors 2013). Most information derived from studies were at low or unclear risk of bias and the certainty of evidence was rated moderate for the outcomes. Hence, the study results should be interpreted with caution despite the effective intervention.

Discussion

This literature review on interventions to enhance adherence to medications in cardiovascular care has highlighted several methods and the varying effectiveness of various approaches that offer insights for future intervention development. Evidence for effectiveness of such interventions was inconsistent, due at least in part to the considerable differences in cardiac disease populations and adherence measurement methods used in these studies. Motivational interviewing, either alone or combined with another adherence approach such as phone or message educational and reminder, appeared the most promising behavioural intervention in improving adherence, having potential for wider application in patients with cardiac disease.

The interventions that utilised motivational interview strategies showed successful steady maintenance of medication adherence over time among hypertension patients (Ogedegbe *et al*. 2008) and improved adherence at 6 months for these patients (Ma *et al*. 2014). These strategies set realistic and specific goals for behaviour modification and prompted patients to follow the plan for behaviour change. The results were in agreement with those of previous studies, which demonstrated that motivational interviewing (MINT) may be a useful approach for addressing medication adherence (DiIorio *et al*. 2008). MINTs were almost uniformly effective and were a fairly homogenous group in both the nature of the services rendered and in duration of follow-up. MINTs entailed enhancing patient readiness to change, increasing their confidence toward ability to overcome barriers, and increased self-motivation to achieve desired outcomes (Rollnick and Miller 1995). These can be achieved when trained nurses integrate adherence behaviour into the patients' daily routines and reinforce the positive effect of MINT by follow-up using phone calls, text messaging, or mails as a mean of multifactorial intervention.

A multifaceted intervention demonstrated statistically significant improvement in medication adherence (Ho *et al*. 2014). The results of this study were consistent with other successful multifaceted interventional studies, which have included medication review with a specific focus on regimen simplification (Bernsten *et al*. 2001), individualised patient education combined with medication reminders (medication chart) (Hawe and Higgins 1990), or a dose administration aid (Lee *et al*. 2006). These results were also in accordance with a study (Edworthy *et al*. 2007) that found significant improvement in adherence for both beta-blocking and lipid-lowering agents with counselling by nurses and pharmacists along with video, printed material, and phone follow-up. Multifaceted interventions demonstrated potentially promising results, but it was difficult to draw conclusions in favour of any particular combination of interventions or intensity because of heterogeneity and complexity

of interventions and multiple adherence measures (Topinková *et al*. 2012), and the great diversity in drug classes considered (van Eijken *et al*. 2003). The cost of these interventions was also an important consideration in the decision of whether or not they should be applied more widely but this could be difficult to determine because components of the interventions overlapped and were not described in sufficient details.

A common element of many medication adherence interventions was education. However, the effectiveness of medication adherence education was varied and the methods of delivered it were with different multi-component which leads to significant and non-significant outcomes. Few studies were demonstrated effective nurse-based medication educational interventions includes six monthly face to face education sessions (Hacihasanoğlu and Goözuöm 2011) about the important of regular medication taking, medication efficacy, possible side effects, and the importance of follow-up visits. Another study proven effective medication education combined with multifaceted elements by sending automatic voice messages at one week and one months after hospital discharge for medication reminder and refill for 12 months (Ho *et al*. 2014). On the contrary, a written medication educational materials delivered by a nurse combined with three structured counselling sessions was not associated with a significant improvement of medication adherence (Beune *et al*. 2014).

Comparisons across assessments of adherence was also difficult. The medication event monitoring system (MEMS), one of the most reliable objective assessment methods was expensive and not readily available for some dose forms (Remington *et al*. 2007, van den Boogaard *et al*. 2011). Self-reporting, which is known as feasible and cheap, was a common method of measuring medication adherence. Subjective self-reporting measures can be relatively simple to use and are less expensive, a number are well-validated and have been strongly correlated with objective measures of adherence in different populations (Nguyen *et al*. 2014).

For text and mail message interventions, studies showed similar improvement in medication adherence at 16% (Wald *et al*. 2014) and 17% (Smith *et al*. 2008), respectively. These findings are consistent with those of recent RCTs reporting that bidirectional text messages resulted in statistically significant improvement in anti-retroviral treatment adherence among patients with Human Immunodeficiency Virus (HIV) (Lester *et al*. 2010) and with hypertension (Márquez Contreras *et al*. 2005). Similarly, phone call interventions significantly improved adherence self-efficacy to antihypertensive medications in the intervention groups at 10 months follow-up, when combined with health promotion theory-based medication education and behavioural modification targeting patients' life styles (Hacihasanoğlu and Goözuöm 2011). A review (Cutrona *et al*. 2010) concluded that phone calls both by trained lay people and by a nurse yielded significant improvements in cardiovascular adherence. Likewise, tailored telephone call nursing interventions reduced the time commitment for the primary care provider, lowered system and provider costs, and showed success in improving medication adherence for patients with chronic diseases (Bosworth *et al*. 2009). However, in the Rinfret *et al*. (2013) study, both intervention and control groups had high medication adherence at follow-up, which meant findings may have been overestimated and may not be generalizable to other cardiac populations. Further, a review by Mansoor *et al*. (2013) found that informational interventions had little or no impact on improving medication adherence. This could be due to several reasons, including how well health care providers delivered the interventions, the patient groups, study design and differences in the relative contribution of each element to the intervention. For example, information supplied passively to the patient may not be adequate, and the additional element of requiring a response from the patient may be what was responsible for significant change. All in all, using technology in the form of phone message intervention provided by nurses

appeared feasible, cost-effective and an effective tool to improve medication adherence in resource-limited settings.

The results of nurse-led interventions were mixed and overall not encouraging although one study (Nieuwkerk *et al*. 2012) was successful in increasing adherence rates for lipid-lowering medications by enhancing patients' knowledge through structured counselling sessions. A similar intervention was shown to be beneficial in patients with hypertension (Logan *et al*. 1983). Nurse-led interventions have also failed to show positive effects on medication adherence in other populations. For example Clarke *et al*. (2002) found no significant between-group differences in mean change scores of medicine taking after 12 months of a nurse-led diabetes management program. However, overall, the evidence is not adequate and has not addressed factors such as long-term medication adherence, with current studies limited by short follow-up, small sample size, and inconsistent adherence measures.

To date, of nurse-delivered interventions to improve adherence to cardiovascular medications, multifaceted interventions appear to offer the best opportunities to optimise medication adherence, with component behavioural interventions in the form of motivational interviewing, educational content, text and/or phone messaging showing the greatest success.

Conclusion

The prevalence of CVD is rapidly rising worldwide with emerging new and complex medication regimens which challenge both patients and healthcare providers (Hauptman 2008). Healthcare providers in primary and secondary health settings should maximise the health benefits offered by medications by adopting those strategies shown to be effective at enhancing patients' adherence to their medications. Researchers should clearly justify and specify methodologies to generate a cumulative body of knowledge that can be used to inform clinical practice. This review has demonstrated the need for application of more

rigorous methods to test the effectiveness of adherence interventions, addressing issues of study design (e.g. use of RCT), sampling (low-adherence patients) and choosing effective and feasible adherence measures. Combined interventions need to be detailed and employ multiple approaches such as motivational interviewing and education that target the desired behaviour change, and reinforcement of these behaviours with phone or text message strategies. It is imperative that interventions chosen are theory-based, and evaluated in robust trials to demonstrate effects on clinical outcomes, feasibility in usual practice settings, and sustainability. Future research should entail: 1) Patient assessment to identify modifiable deterrents to medication adherence (e.g. low self-efficacy or patient beliefs about medication efficiency); 2) Identifying and trialling feasible, effective and cost-effective multi-approach interventions, for example motivational interviewing combined with technologies such as phone and text messages; 3) Following patients for longer periods to explore longer term intervention effects; and 4) Applying consistent, reliable, and cost-effective adherence measurement.

Of the interventions intended to improve adherence to cardiovascular medications tested by studies in this review, multi-component interventions, tailored to address the patients' health behaviours, appeared to offer most promise.

References

Australian Institute of Health Welfare (2014), Vol. 2015.

Baroletti, S. & Dell'Orfano, H. (2010) Medication Adherence in Cardiovascular Disease. *Circulation,* **121**(12), 1455-1458.

Bernsten, C., Björkman, I., Caramona, M., Crealey, G., Frøkjær, B., Grundberger, E., Gustafsson, T., Henman, M., Herborg, H. & Hughes, C. (2001) Improving the well-being of elderly patients via community pharmacy-based provision of pharmaceutical care. *Drugs & aging,* **18**(1), 63-77.

Beune, E.J.A.J., Moll van Charante, E.P., Beem, L., Mohrs, J., Agyemang, C.O., Ogedegbe, G. & Haafkens, J.A. (2014) Culturally Adapted Hypertension Education (CAHE) to Improve Blood Pressure Control and Treatment Adherence in Patients of African Origin with Uncontrolled Hypertension: Cluster-Randomized Trial. *PLoS ONE,* **9**(3), e90103.

Bosworth, H.B., Olsen, M.K., Dudley, T., Orr, M., Goldstein, M.K., Datta, S.K., McCant, F., Gentry, P., Simel, D.L. & Oddone, E.Z. (2009) Patient education and provider decision support to control blood pressure in primary care: A cluster randomized trial. *The American Heart Journal,* **157**(3), 450-456.

Clarke, J., Crawford, A. & Nash, D.B. (2002) Evaluation of a comprehensive diabetes disease management program: progress in the struggle for sustained behavior change. *Disease management,* **5**(2), 77-86.

Cutrona, S.L., Choudhry, N.K., Fischer, M.A., Servi, A., Liberman, J.N., Brennan, T. & Shrank, W.H. (2010) Modes of delivery for interventions to improve cardiovascular medication adherence: Review. *The American journal of managed care,* **16**(12), 929-942.

DiIorio, C., McCarty, F., Resnicow, K., Holstad, M.M., Soet, J., Yeager, K., Sharma, S.M., Morisky, D.E. & Lundberg, B. (2008) Using motivational interviewing to promote adherence to antiretroviral medications: A randomized controlled study. *AIDS care,* **20**(3), 273-283.

Edworthy, S.M., Baptie, B., Galvin, D., Brant, R.F., Churchill-Smith, T., Manyari, D. & Belenkie, I. (2007) Effects of an enhanced secondary prevention program for patients with heart disease: A prospective randomized trial. *Canadian Journal of Cardiology,* **23**(13), 1066-1072.

EPOC Resources for review authors (2013) Effective Practice and Organisaton of Care (EPOC). Cochrane Effective Practice and Organisation of Care.

Hacihasanoğlu, R. & Goözuöm, S. (2011) The effect of patient education and home monitoring on medication compliance, hypertension management, healthy lifestyle behaviours and BMI in a primary health care setting. *Journal of Clinical Nursing,* **20**(5/6), 692-705.

Hauptman, P. (2008) Medication adherence in heart failure. *Heart Failure Reviews,* **13**(1), 99-106.

Hawe, P. & Higgins, G. (1990) Can medication education improve the drug compliance of the elderly? Evaluation of an in hospital program. *Patient Education and Counseling,* **16**(2), 151-160.

Haynes, R., Yao, X., Degani, A., Kripalani, S., Garg, A. & McDonald, H. (2005) Interventions for enhancing medication adherence. *The Cochrane Library*.

Higgins, J.P. & Green, S. (2008) *Cochrane handbook for systematic reviews of interventions,* Wiley Online Library.

Ho, P.M., Lambert-Kerzner, A., Carey, E.P., Fahdi, I.E., Bryson, C.L., Melnyk, S.D., Bosworth, H.B., Radcliff, T., Davis, R. & Mun, H. (2014) Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. *JAMA internal medicine,* **174**(2), 186-193.

Jiang, X., Sit, J.W. & Wong, T.K.S. (2007) A nurse-led cardiac rehabilitation programme improves health behaviours and cardiac physiological risk parameters: evidence from Chengdu, China. *Journal of Clinical Nursing,* **16**(10), 1886-1897.

Khan, K.S., Ter Riet, G., Glanville, J., Sowden, A.J. & Kleijnen, J. (2001) *Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews,* NHS Centre for Reviews and Dissemination.

Kripalani, S., Schmotzer, B. & Jacobson, T.A. (2012) Improving Medication Adherence through Graphically Enhanced Interventions in Coronary Heart Disease (IMAGE-CHD): a randomized controlled trial. *Journal Of General Internal Medicine,* **27**(12), 1609-1617.

Laba, T.-L., Bleasel, J., Brien, J.-a., Cass, A., Howard, K., Peiris, D., Redfern, J., Salam, A., Usherwood, T. & Jan, S. (2013) Strategies to improve adherence to medications for cardiovascular diseases in socioeconomically disadvantaged populations: a systematic review. *International journal of cardiology,* **167**(6), 2430-2440.

Lee, J.K., Grace, K.A. & Taylor, A.J. (2006) Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *Jama,* **296**(21), 2563-2571.

Leiva, A., Aguiló, A., Fajó-Pascual, M., Moreno, L., Martín, M.C., Garcia, E.M., Duro, R.E., Serra, F., Dagosto, P., Iglesias-Iglesias, A.A., Company, R.M., Yañez, A., Llobera, J. & On behalf of The Adherence, G. (2014) Efficacy of a brief multifactorial adherence-based intervention in reducing blood pressure: a randomized clinical trial. *Patient preference and adherence,* **8**, 1683-1690.

Lester, R.T., Ritvo, P., Mills, E.J., Kariri, A., Karanja, S., Chung, M.H., Jack, W., Habyarimana, J., Sadatsafavi, M., Najafzadeh, M., Marra, C.A., Estambale, B., Ngugi, E., Ball, T.B., Thabane, L., Gelmon, L.J., Kimani, J., Ackers, M. & Plummer, F.A. (2010) Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *The Lancet,* **376**(9755), 1838-45.

Logan, A.G., Milne, B., Flanagan, P. & Haynes, R. (1983) Clinical effectiveness and cost-effectiveness of monitoring blood pressure of hypertensive employees at work. *Hypertension,* **5**(6), 828-836.

Ma, C., Zhou, Y., Zhou, W. & Huang, C. (2014) Evaluation of the effect of motivational interviewing counselling on hypertension care. *Patient Education and Counseling,* **95**(2), 231-237.

Mansoor, S.M., Krass, I. & Aslani, P. (2013) Multiprofessional interventions to improve patient adherence to cardiovascular medications. *Journal Of Cardiovascular Pharmacology And Therapeutics,* **18**(1), 19-30.

Márquez Contreras, E., Vegazo García, O., Martel Claros, N., Gil Guillén, V., de la Figuera von Wichmann, M., Casado Martínez, J.J. & Fernández, R. (2005) Efficacy of telephone and mail intervention in patient compliance with antihypertensive drugs in hypertension. ETECUM-HTA study. *Blood Pressure,* **14**(3), 151-158.

McKenzie, S., McLaughlin, D., Clark, J. & Doi, S.R. (2015) The Burden of Non-Adherence to Cardiovascular Medications Among the Aging Population in Australia: A Meta-Analysis. *Drugs & Aging,* **32**(3), 217-225.

Menditto, E., Guerriero, F., Orlando, V., Crola, C., Di Somma, C., Illario, M., Morisky, D.E. & Colao, A. (2015) Self-Assessment of Adherence to Medication: A Case Study in Campania Region Community-Dwelling Population. *Journal of Aging Research,* **2015**, 682503.

Moher, D., Liberati, A., Tetzlaff, J. & Altman, D.G. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals Of Internal Medicine,* **151**(4), 264.

Nguyen, T.M.U., Caze, A.L. & Cottrell, N. (2014) What are validated self-report adherence scales really measuring?: a systematic review. *British journal of clinical pharmacology,* **77**(3), 427-445.

Nieuwkerk, P.T., Nierman, M.C., Vissers, M.N., Locadia, M., Greggers-Peusch, P., Knape, L.P.M., Kastelein, J.J.P., Sprangers, M.A.G., de Haes, H.C. & Stroes, E.S.G. (2012) Intervention to Improve Adherence to Lipid-Lowering Medication and Lipid-Levels in Patients With an Increased Cardiovascular Risk. *The American Journal of Cardiology,* **110**(5), 666-672.

Nieuwlaat, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C & B, H.R. (2014) Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews,* (11).

Ogedegbe, G., Chaplin, W., Schoenthaler, A., Statman, D., Berger, D., Richardson, T., Phillips, E., Spencer, J. & Allegrante, J.P. (2008) A practice-based trial of motivational interviewing and adherence in hypertensive African Americans. *American journal of hypertension,* **21**(10), 1137-1143.

Okrainec, K., Banerjee, D.K. & Eisenberg, M.J. (2004) Coronary artery disease in the developing world. *American heart journal,* **148**(1), 7-15.

Poluzzi, E., Piccinni, C., Carta, P., Puccini, A., Lanzoni, M., Motola, D., Vaccheri, A., De Ponti, F. & Montanaro, N. (2011) Cardiovascular events in statin recipients: impact of adherence to treatment in a 3-year record linkage study. *European journal of clinical pharmacology,* **67**(4), 407-414.

Remington, G., Kwon, J., Collins, A., Laporte, D., Mann, S. & Christensen, B. (2007) The use of electronic monitoring (MEMS®) to evaluate antipsychotic compliance in outpatients with schizophrenia. *Schizophrenia Research,* **90**(1–3), 229-237.

Rinfret, S., Rodés-Cabau, J., Bagur, R., Déry, J.-P., Dorais, M., Larose, É., Barbeau, G., Gleeton, O., Nguyen, C.-M., Noël, B., Proulx, G., Roy, L., Taillon, I., De Larochellière, R., Bertrand, O.F. & Investigators, f.t.E.-I. (2013) Telephone contact to improve adherence to dual antiplatelet therapy after drug-eluting stent implantation. *Heart,* **99**(8), 562-569.

Rollnick, S. & Miller, W.R. (1995) What is motivational interviewing? *Behavioural and cognitive psychotherapy,* **23**(04), 325-334.

Sabaté, E. (2003) *Adherence to long-term therapies: evidence for action*, Geneva, Switzerland: World Health Organisation.

Schroeder, K., Fahey, T., Hollinghurst, S. & Peters, T.J. (2005) Nurse-led adherence support in hypertension: a randomized controlled trial. *Family Practice,* **22**(2), 144-151.

Simons, L.A., Ortiz, M. & Calcino, G. (2011) Long term persistence with statin therapy: Experience in Australia 2006-2010. *Australian Family Physician,* **40**(5), 319-22.

Smith, D.H., Kramer, J.M., Perrin, N., Platt, R., Roblin, D.W., Lane, K., Goodman, M., Nelson, W.W., Yang, X. & Soumerai, S.B. (2008) A randomized trial of direct-to-patient communication to

enhance adherence to β-blocker therapy following myocardial infarction. *Archives of internal medicine,* **168**(5), 477-483.

Topinková, E., Baeyens, J.P., Michel, J.-P. & Lang, P.-O. (2012) Evidence-Based Strategies for the Optimization of Pharmacotherapy in Older People. *Drugs & Aging,* **29**(6), 477-494.

van Dalem, J., Krass, I. & Aslani, P. (2012) Interventions promoting adherence to cardiovascular medicines. *International Journal of Clinical Pharmacy,* **34**(2), 295-311.

van den Boogaard, J., Lyimo, R.A., Boeree, M.J., Kibiki, G.S. & Aarnoutse, R.E. (2011) Electronic monitoring of treatment adherence and validation of alternative adherence measures in tuberculosis patients: a pilot study. *Control electrónico del cumplimiento terapéutico de pacientes con tuberculosis y validación de medidas alternativas de cumplimiento: estudio piloto.,* **89**(9), 632-639.

van Eijken, M., Tsang, S., Wensing, M., de Smet, P.A.G.M. & Grol, R.P.T.M. (2003) Interventions to improve medication compliance in older patients living in the community: a systematic review of the literature. *Drugs & Aging,* **20**(3), 229-240.

Wald, D.S., Bestwick, J.P., Raiman, L., Brendell, R. & Wald, N.J. (2014) Randomised Trial of Text Messaging on Adherence to Cardiovascular Preventive Treatment (INTERACT Trial). *PLoS ONE,* **9**(12), e114268.

Wilke, T., Müller, S. & Morisky, D.E. (2011) Toward Identifying the Causes and Combinations of Causes Increasing the Risks of Nonadherence to Medical Regimens: Combined Results of Two German Self-Report Surveys. *Value in Health,* **14**(8), 1092-1100.

World Health Organization (2004) Atlas of Heart Disease and Stroke. Vol. 2015 WHO, Geneva.