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By Mieke van Driel

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Cochrane Corner: Interventions to improve adherence to lipid-lowering medication

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BACKGROUND

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High cholesterol is one of the top 10 risk factors accounting for more than one-third of all deaths worldwide, estimated to cause 18% of cerebrovascular disease (CVD) and 56% of ischaemic heart disease (IHD) (1).

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There is compelling evidence that lipid-lowering drugs can reduce both lipid levels and the risk of heart attacks and strokes. Lipid-lowering medications include statins, fibrates, niacin, and bile acid resins. Large randomised trials and meta-analyses support the effectiveness of statins (2,3) showing an approximately linear relationship between the absolute reduction in LDL-cholesterol and proportional reductions in the incidence of coronary and major vascular

events (2). Statins are recommended as first-line therapy, whereas fibrates, niacin and bile acid resins can be considered as second-line therapy or in combination with statins (4,5).

Despite this evidence and the availability of guidelines, lipid-lowering therapy is still underused. Although recommendations about drug treatments vary from country to country, they generally recommend statin treatment in people with clinical evidence of CVD to reduce further ischaemic events. For primary prevention of CVD, lipid-lowering medication is recommended in adults who have a 20% or greater risk of developing CVD in the next 10 years (4). Recommendations by the American College of Cardiology/American Heart Association have recently broadened the indications for lipid-lowering therapy, adding to the challenge of ensuring adequate treatment coverage (5).

Adherence to treatment is important for optimal effectiveness. Adherence is defined as the extent to which people take medication as prescribed. Poor adherence is determined by a variety of factors such as lack of knowledge, denial, adverse effects, poor memory, and adverse attitudes to treatment. Interventions to improve adherence to medication can focus on the person (patient education), the drug regimen (simplification of regimens), the physician (decision making aids) or the health system (delivery of medication). A systematic review has shown that adherence to short-term drug treatment can be improved by written information, personal phone calls and counselling, but more complex interventions are needed for long-term treatments (6). Treating a symptomless condition like hyperlipidaemia poses a particular challenge. A previous version of this Cochrane review did not show a clear benefit of any particular method (7). We have updated this review with recent evidence to assess the effectiveness of these methods, including new interventions derived from advancements in recent technology, on clinical outcomes in patients prescribed lipid-lowering treatment (8).

REVIEW METHODS

We reviewed randomised controlled trials of interventions to increase adherence for lipid-lowering medication in adults in ambulatory settings looking at adherence to treatment (primary outcome) as well as changes to serum lipid levels, health outcomes such as quality

of life, morbidity and mortality, and adverse effects (secondary outcomes). We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, and CINAHL up to 3 February 2016, and clinical trials registers (ANZCTR and ClinicalTrials.gov) up to 27 July 2016. We used standard Cochrane methods to select studies, extract data, and assess risk of bias for each of the included studies. We used GRADEPro to rate the quality of the overall effect estimates. We reported dichotomous data as odds ratios (ORs) with 95% confidence intervals (CIs) and continuous data as mean difference (MD) with standard deviation (SD) of pre- and post-measurements. Serum cholesterol values are reported in mg/dL, using the formula: 1 mmol/l = 38.66976 mg/dL.

We grouped the studies in seven types of interventions: 1) Simplification of drug regimen; 2) Patient education and information; 3) Intensified patient care; 4) Complex behavioural approaches; 5) Decision support systems; 6) Administrative improvements; and 7) Pharmacy-led interventions. 'Usual care' was not defined as a separate intervention. We pooled data with a random-effects model, using a per-protocol analysis, as intention-to-treat analysis would yield misleading results by not showing an effect in many of these studies due to the pragmatic nature of the study designs.

We performed sensitivity analysis to assess the impact of heterogeneity and compared random-effects versus fixed-effects models to assess the robustness of the effect estimates. We also assessed the impact of attrition on the overall study outcome by removing studies with high attrition (> 20%).

MAIN RESULTS

We included 35 studies, randomising 925,171 participants. We pooled seven studies with 11,204 individuals that compared adherence rates of those in an intensification of patient care intervention (e.g. combinations of the following: electronic reminders, pharmacist-led interventions, healthcare professional education of patients) versus usual care over the short term (≤ 6 months). Participants in the intervention group had better adherence than those receiving usual care (odds ratio (OR) 1.93, 95% confidence interval (CI) 1.29-2.88; 7

studies; 11,204 participants; moderate-quality evidence). A separate analysis showed improvements in long-term adherence rates (>6 months) using intensification of care (OR 2.87, 95% CI 1.91-4.29; 3 studies; 663 participants; high-quality evidence). Analyses of the effect on total cholesterol and LDL-cholesterol levels also showed a positive effect of intensified interventions over both short- and long-term follow-up. Over the short term, total cholesterol decreased by a mean of 17.15 mg/dL (95% CI 1.17-33.14; 4 studies; 430 participants; low-quality evidence) and LDL-cholesterol decreased by a mean of 19.51 mg/dL (95% CI 8.51-30.51; 3 studies; 333 participants; moderate-quality evidence). Over the long term (>6 months) total cholesterol decreased by a mean of 17.57 mg/dL (95% CI 14.95-20.19; 2 studies; 127 participants; high-quality evidence). Included studies did not report usable data for quality of life, morbidity and mortality, adverse effects or costs. Sensitivity analyses confirmed the robustness of these findings.

LIMITATIONS OF THE EVIDENCE

In general, the risk of bias was low for selection, attrition, and reporting bias. There was unclear risk of bias relating to blinding for most studies. The nature of the majority of interventions implies that blinding of participants was not possible (e.g. reminder phone calls or education sessions). As this is acceptable in a pragmatic context, we have not downgraded the evidence for lack of blinding. In studies using a fixed dose combination or 'polypill' blinding is feasible, but we could not pool them in our review. We graded the evidence for long-term adherence and reduction in total cholesterol as high quality. We downgraded the evidence for short-term outcomes (patient adherence and LDL-cholesterol) to moderate quality due to heterogeneity and the short-term outcome of total serum cholesterol to low quality due to heterogeneity and a wide confidence interval (imprecision).

IMPLICATION FOR PRACTICE

Our review indicates that interventions classified as intensification of patient care could improve both short-term and long-term adherence rates and serum cholesterol levels when compared to usual care (8). Given the importance of statin therapy, strategies to improve

adherence rates could have significant benefit in those people for whom statins are recommended. The successful intensification of patient care interventions typically involved strategies beyond what a single clinician could provide. Instead, healthcare delivery systems might be better equipped to deliver a combination of these types of interventions, i.e. pharmacist-led interventions, multidisciplinary education or counselling, and automated reminders, along with a focus on teamwork with the primary care physician to provide the best potential for effectiveness.

The results of our meta-analysis must, however, be seen in the context of the healthcare systems in which they were trialled. For instance, pharmacy-led interventions are applicable in systems with a strong and well-structured medication delivery system through pharmacies, but will not be feasible in, for instance, low income countries where drug dispensing is much less controlled or not integrated into the healthcare system. Cultural and social context plays a role and the impact of automated reminders delivered as text messages may be less effective if patients' beliefs regarding their medicines have not been addressed.

4 It is important to acknowledge the wide diversity of control interventions that we grouped as 'usual care', e.g. pharmacy usual care can include patient education in some settings but none at all in others. Likewise, usual care in the context of physician-delivered interventions can also vary extensively. The results of our comparisons therefore need to be interpreted with caution.

Implications for research

2 Adherence is a complex concept and it seems reasonable for interventions to address this complexity with a more patient-centred approach. People's beliefs and preferences must be acknowledged and incorporated into adherence-enhancing interventions. A combination of strategies including education, reminders, adherence reinforcement and emphasis on the person's perspective might be more effective. Future studies should use validated methods for measuring adherence and assessing the effects on serum lipid levels. Long-term follow-up, of 12 months and more, will reveal a more realistic picture of adherence to life-long treatment. Finally, studies evaluating outcomes such as morbidity, mortality, quality of life

and cost effectiveness are needed in order to provide guidance to clinicians and healthcare systems.

Competing interests

None

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Table 1: Summary of Findings for the comparison of intensified patient care vs usual care.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with usual care	Risk with Intensified patient care			
Medication adherence at ≤ 6 months	Study population		OR 1.93 (1.29 to 2.88)	11,204 (7 RCTs)	⊕⊕⊕⊕ ¹ MODERATE
	456 per 1,000	618 per 1,000 (519 to 707)			
Medication adherence at > 6 months	Study population		OR 2.87 (1.91 to 4.29)	663 (3 RCTs)	⊕⊕⊕⊕ HIGH
	705 per 1,000	873 per 1,000 (820 to 911)			
Reduction in LDL-C at ≤ 6 months (mg/dL)	Mean reduction in LDL-C at ≤ 6 months (mg/dL) was 0	Mean reduction in LDL-C at ≤ 6 months (mg/dL) in the intervention group was 19.51 greater (8.51 greater to 30.51 greater)	-	333 (3 RCTs)	⊕⊕⊕⊕ ¹ MODERATE
Reduction in total serum cholesterol at ≤ 6 months (mg/dL)	Mean reduction in total serum cholesterol at ≤ 6 mos (mg/dL) was 0	Mean reduction in total serum cholesterol at ≤ 6 months (mg/dL) in the intervention group was 17.15 greater (1.17 greater to 33.14 greater)	-	430 (4 RCTs)	⊕⊕⊕⊖ ^{1,2} LOW
Reduction in total serum cholesterol at > 6 mos (mg/dL)	Mean reduction in total serum cholesterol at > 6 months (mg/dL) was 0	Mean reduction in total serum cholesterol at > 6 months (mg/dL) in the intervention group was 17.57 greater (14.95 greater to 20.19 greater)	-	127 (2 RCTs)	⊕⊕⊕⊕ HIGH

GRADE Working Group grades of evidence.

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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.

Very low quality: we are very uncertain about the estimate.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

¹ Downgraded due to heterogeneity

² Downgraded due to wide confidence interval

Table 2: Overview of included studies and their comparisons.

Number of Studies	Number of participants randomised	Description of interventions	Reported outcomes	Pooled outcomes	Comments
<i>Simplification of drug regimen vs placebo/usual care</i>					
7	4,342	5 studies: Fixed-dose combination (FDC or 'polypill'); 2 studies: Reduction of daily dosing	Adherence; Total cholesterol; LDL-C; HDL-C	4/5 studies with FDC found improved adherence; Reduced daily dosing did not improve adherence	Outcomes could not be pooled; Outcomes reported for 4320 participants
<i>Patient education vs usual care</i>					
5	9,421	Pharmacist-provided information (videotapes, booklets, educational newsletters, telephone follow up)	Adherence; LDL-C	Not consistent improvement in adherence or cholesterol	Outcomes could not be pooled; Outcomes reported for 8116 participants
<i>Intensified patient care vs usual care</i>					
16	22,785	Written postal material, telephone or other reminders	Adherence; Total cholesterol; LDL-C	≤6 months: Adherence OR 1.93 (1.29-2.88); TC mean difference (MD) 17.15 (1.17-33.14); >6 months: Adherence OR 2.87 (1.91-4.29); TC MD 17.57 (14.95-20.19)	Outcomes reported for 13,602 participants
<i>Complex behavioural approaches vs usual care</i>					
1	110	Small-group training followed by postal information	Adherence; Total cholesterol; LDL-C; HDL-C	Adherence not improved; HDL-C improved	Outcomes could not be pooled; Outcomes reported for 108 participants
<i>Decision support systems vs usual care/complex behavioural approaches</i>					
2	2,490	Adherence information and motivational interviewing	Adherence; LDL-C	Adherence not improved; LDL-C not improved	Outcomes could not be pooled; Outcomes reported for 2,073 participants
<i>Administrative improvements vs usual care</i>					
2	8,148	1 study: participant's drug profile provided to prescriber (incl. costs of medications dispensed, out-of-pocket expenditure, graphic of unfilled prescriptions, and days of drug supply); if treatment	Adherence; costs	Adherence improved in 1 study; costs to healthcare system not different, costs to patients reduced in 1 study	Outcomes could not be pooled; Outcomes reported for 7,509 participants

		adherence <80% alert to check with the participant; 1 study: medication co-payments waived at pharmacy (control group continued to pay co-payments)			
<i>Pharmacy-led interventions vs usual care</i>					
2	878,274	Automated phone calls on days 3 and 7 if prescription remained unpurchased or calls from pharmacist if prescription was not picked up after 8 days; automated phone reminders if refill (over)due	Adherence; LDL-C	Adherence not different; LDL-C reduced (1 study)	Outcomes could not be pooled; Outcomes reported for 878,260 participants

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