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Title: Multi-modal interventions to enhance adherence to secondary preventive medication after stroke: a systematic review and meta-analyses.

Head title: Adherence to Stroke Secondary Preventative Drugs

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Abstract

Introduction

Non-adherence to secondary preventative medications after stroke is common and is associated with poor outcomes. Numerous strategies exist to promote adherence. We performed a systematic review and meta-analysis to describe the efficacy of strategies to improve adherence to stroke secondary prevention.

Methods

We created a sensitive search strategy and searched multiple electronic databases (MEDLINE, EMBASE, CINAHL, PsycINFO, CENTRAL, and Web of Knowledge) for studies of interventions that aimed to enhance adherence to secondary preventative medication after stroke. We assessed quality of included studies using the Cochrane tool for assessing risk of bias. We performed narrative review and performed meta-analysis where data allowed.

Results

From 12,237 titles, we included seventeen studies in our review. Eleven studies were considered to have high risk of bias, 3 with unclear risk and 3 of low risk. Meta-analysis of available data suggested that these interventions improved adherence to individual medication classes (blood pressure lowering drugs - OR, 2.21; 95% CI (1.63, 2.98), [p<0.001], lipid-lowering drugs - OR, 2.11; 95% CI (1.00, 4.46), [p=0.049], and anti-thrombotic drugs – OR, 2.32; 95% CI (1.18, 4.56, [p=0.014]) but did not improve adherence to an overall secondary preventative medication regimen (OR, 1.96; 95% CI (0.50, 7.67), [p=0.332]).

Conclusion

Interventions can lead to improvement in adherence to secondary preventative medication after stroke. However, existing data is limited as several interventions, duration of follow-up, and various definitions were used. These findings need to be interpreted with caution.

Keywords: Stroke, TIA, secondary, prevention, intervention, adherence.

Introduction

A variety of evidence based pharmacological strategies are recommended to reduce the risk of stroke recurrence. The exact medications used will differ dependent on stroke aetiology and typically include anti-thrombotic(1-4), blood pressure lowering(4-7) and lipid lowering(4, 8, 9) strategies for ischaemic stroke and blood pressure lowering(5, 10) strategies for haemorrhagic stroke. It is recognised that adherence to secondary preventative medications after stroke is variable; in some studies more than half of participants stopped taking their prescribed drugs 1 year after the stroke incident(11).

There are many phrases used to describe the process of patients taking medication according to a prescribed schedule, for example adherence, compliance, concordance. For consistency we will use the term medication adherence throughout the review. We recognise that this descriptor is problematic but there is no preferred terminology and medication adherence is the phrase often used in the scientific literature.

Several interventions have been tested to improve adherence to prescribed medication, thus, a specific review of this area was required. We performed a systematic review and meta-analysis of interventions designed to improve adherence to preventative medications in patients with stroke.

Methodology

We conducted a systematic review and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines(12). The review protocol was registered in PROSPERO (registration number, CRD42015027529).

Search Strategy and Study Selection

We created lists with all identifiable synonyms for "Stroke" and "Medication Adherence" (available in the supplementary materials). Then, two independent reviewers (SA and WD) searched MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCOhost), PsycINFO (EBSCOhost), CENTRAL (Cochrane Library), and Web of Knowledge (Thomson Reuters). We also reviewed reference lists of included studies and relevant reviews to identify further studies. We continued the process until no further papers were identified.

Eligibility Criteria

We included interventional studies published in English. Abstracts of unpublished papers were excluded. Studies had to include adult participants (aged 18 years or more) who had previously suffered stroke or transient ischaemic attack (TIA) and who were prescribed medication for the prevention of recurrent stroke. We defined preventative medications as any antiplatelet, anticoagulant, blood pressure lowering or lipid lowering drugs. Studies had to report a measure of medication adherence as an outcome. We recognised that many interventions can potentially impact on adherence. We were inclusive and accepted any study where the authors' stated primary aim was to improve adherence. We accepted any control, including usual care and sham interventions. Where disagreement arose regarding study eligibility, a third party review (JD) and consensus meeting was arranged.

Assessment of Risk of Bias

We used the Cochrane tool for assessing risk of bias which is a domain-based evaluation tool for parallel-group trials(13) and modified to fit the few studies where an alternative design was used. Two reviewers (SA and JD) independently assessed risk of bias and met to discuss and finalise the assessment where disagreement arose. We considered studies as of high overall risk of bias if they did not meet the criteria specified for more than two key domains (selection, performance or detection bias). Moreover, given the nature of the studies we

acknowledged that blinding of the participant was rarely practical so we did not judge studies as of high risk of bias based on blinding only.

Narrative Review and Statistical Analysis

We described study characteristics and interventions using narrative review. Where possible, effect and sample size for outcomes relating to medication adherence were extracted and combined within a meta-analysis to derive an odds ratio and 95% confidence interval (CI) for the effect of the intervention. Forest plots were constructed for each analysis (overall medication, blood pressure-lowering drugs, lipids-lowering drugs and anti-thrombotic medication each in a separate analysis). Studies included in the overall medication analysis were those that assessed the effect of an intervention on the adherence to entire medication regimen prescribed after stroke. We have assessed heterogeneity using Higgin I^2 (13) and repeated analyses where heterogeneity was detected with one study removed. We assessed for publication bias using funnel plots (available in supplementary appendix). Comprehensive Meta-Analysis (CMA, version 2.0, Biostat Inc, Englewood, New Jersey, US) software was used for all analyses.

Results

The search encompassed the literature up to an including April 2014 and identified a total of 12,237 titles. Title review identified 143 papers for abstract review. Of these 57 were retrieved for full-text review. We identified 17 of these as meeting our eligibility criteria (figure 1). The completed PRISMA Checklist is available in supplementary materials.

Narrative Review

Description of Eligible Studies

The 17 included studies were prospective interventional studies published between 2004 and 2014, of which 8 used a single group (pre- and post-intervention) design(14-21) and 9 compared two groups(22-30). Details of study characteristics and interventions can be found in table 1.

The total number of participants enrolled into the included studies was 3942 with stroke/TIA. Of these, 2090 participants were in an intervention group and 824 participants were controls. Details of participants can be found in the supplementary materials.

Description of Interventions

Interventions were educational and motivational as described in 6 studies(20, 23-25, 27, 29). Patients were prescribed medication and educated about it while in-patient not in primary care in three studies(19-21). Three studies targeted simplification of drug regimen(14, 15, 26), two of which provided dosettes(15, 26). One study provided environmental cues or reminders together with reducing concerns and misbeliefs regarding medications(28). Five studies used programs of combined interventions to enhance risk factor management after stroke (e.g. STOP Program(22); PROTECT Program(16-18); STOP stroke Program(30)).

Secondary Preventative Drug Classes

Ten studies assessed adherence to anti-thrombotics(14, 16-18, 20, 21, 23, 25, 27, 30), ten looked at anti-hypertensive medications(15-18, 20, 24, 25, 27, 28, 30), ten studies explored lipid-lowering drugs(15-20, 23, 25, 27, 30) and seven looked at adherence to the overall medications regimen(21-23, 26-29).

Method of Assessing Adherence to Medications

Ten studies used a subjective measure only (telephone or face-to-face interviews, or questionnaires)(14, 16-18, 20-22, 24, 29, 30). Two studies used an indirect measure where

Primary Care Physician was contacted in one(23) and the other used measurement of blood pressure and cholesterol(25). Remaining five studies used mixed methodology to assess medication adherence (i.e. subjective and objective measures)(15, 19, 26-28).

Efficacy of Interventions

Interventions used in 3 studies were beneficial and resulted in statistically significant improvement in medication adherence(16, 23, 29). The interventions of 3 other studies were helpful in improving adherence but not to all measured adherence aspects(15, 20, 28) and the interventions in 4 studies were neutral and resulted in no difference between groups(24, 26, 27, 30).

Beneficial Interventions

Interventions that involved patient counselling and education at discharge improved adherence to antithrombotic drugs (83.8% control vs. 91.9% intervention [P=0.033]), statins (69.8% control vs. 87.7% intervention [P<0.001]) and the overall regimen (83.3% control vs. 90.9% intervention [P=0.01])(23). A study adopted an educational program to manage risk factors after patient discharge and that resulted in a statistically significant improvement in adherence to antihypertensive (from 61.7% to 77.6%), antiplatelet (from 50.1% to 95.7%) and lipid-lowering drugs (from 39.8% to 81.2%) [all p values <0.05](16). Another study encouraged self-care after stroke which resulted in a statistically significant improvement in medication adherence between intervention (p<0.001) and control group (p=0.293)(29).

A motivational intervention piloted to support health behaviour change was statistically significant in improving medication adherence (25% non-adherers before vs. 15% after intervention [p=0.003])(15) but not adherence reported by pharmacist. Another study assessed rate of medication adherence using electronic medication monitoring and provided

environmental cues as reminders to take medications(28). Medication adherence using the MARS questionnaire improved by a mean difference: 0.61; 95% CI (0.1, 1.2) [p=0.027]). This intervention also resulted in improved rate of taking doses as scheduled (mean difference: 9.8%; 95% CI (0.2, 16.2) [p=0.048]) but not total doses taken nor days when correct dose taken. Patients in another study were initiated therapy with secondary preventative medication at discharge and educated regarding their medication then followed-up annually(20). This intervention resulted in a statistically significant persistence to antihypertensive (from 58% at discharge to 74% 10 years after stroke) and lipid-lowering drugs (21% to 48%) but declined persistence for antithrombotic drugs (from 92% to 78%) (all p values <0.001).

Interventions with No Difference

A motivational and educational intervention in one of the studies was not effective in improving medication compliance (99% control versus 98% intervention [p=0.496])(24). Another study that targeted blood pressure management after stroke did not differ in medication self-efficacy (p=0.28), number of missed pills (p=0.95), or adherence reported by community pharmacist (p=0.15)(26). STOP Stroke Program was a motivational intervention to modify patients' and caregivers' behaviour after stroke but resulted in no difference in patients' adherence to medication(30). Researchers in another study adopted a behaviour modification technique and this intervention did not improve adherence rate to antiplatelet drugs (p=0.28), antihypertensive drugs (p=0.81) or statins (p=0.92)(27).

The remaining seven studies(14, 17-19, 21, 22, 25) did not report the significance level of their intervention in quantitative terms although(17-19, 21, 22) claimed the intervention was effective in improving medication adherence. The supplementary materials contains more details of outcomes.

Risk of Bias across Included Studies

Eleven studies were felt to be of high risk mainly because of selection, performance or detection bias(14-21, 23, 28, 29). Nine studies were non-randomised or did not follow an adequate randomisation method(14-21, 29). Eleven did not mask participants' allocation(14-21, 23, 28, 29). Participants and personnel were not blinded in thirteen(14-21, 23, 24, 28-30) and the outcome assessors were not blinded in eight studies(14, 16-19, 21, 23, 28). Fifteen studies used a subjective method to monitor adherence five of which combined it with other measures, this self-reported adherence is questionable as it is subject to bias and reported to overestimate adherence(31, 32). More details on other sources of bias in included studies are available in the supplementary materials.

Meta-Analysis

We separated findings of included studies depending on secondary preventative medication classes reported (table 2). Four studies were included in the meta-analysis of studies reporting effect of intervention on adherence to the overall secondary preventative medications regimen after stroke(22, 23, 27, 28). This analysis showed a non-significant effect of intervention in included studies on adherence to the overall medication regimen (OR, 1.96; 95% CI (0.50, 7.67), [p=0.332]). Higgin I^2 indicated a substantial heterogeneity, so this analysis was performed with one study removed (27) as it was clearly weighting results (forest plot of resulted analysis in supplementary materials). Three studies were excluded from this analysis because two recorded changes in medication adherence based on questionnaire scores (i.e. no effect size measurement available but change in questionnaire scores only and used different scales) (26, 29) and one was non-controlled(21).

Six papers were included in the meta-analysis of studies reported adherence to blood-pressure lowering drugs; three of which used a matched group cohort(15, 16, 18) and three performed two-group analysis(24, 25, 27). This analysis showed a significant effect of intervention within studies used a matched group analysis (OR, 2.21; 95% CI (1.63, 2.98), [p<0.001]) but not those used unmatched groups (OR, 0.966; 95% CI (0.26, 3.59), [p=0.959]). Four studies were excluded from this analysis. One was non-controlled study(20), one only reported change in adherence in terms of questionnaire scores(28), one did not record effect size of intervention directly on medication adherence (30), and one(17) used the same population as another study already included in the analysis(18).

Three studies were included in the meta-analysis of studies reported effect of intervention on adherence to lipid-lowering drugs(23, 25, 27). This meta-analysis showed a significant effect of interventions used in included studies on adherence to lipid-lowering drugs OR, 2.11; 95% CI (1.00, 4.46), [p=0.049]. Seven studies were excluded from this analysis; two were non-controlled(19, 20), two lacked record of effect size of intervention on adherence(15, 30), and two studies used matched group analysis (16, 18) unlike included studies. Also, two studies(17, 18) analysed the same population so(17) was excluded.

Two studies were included in the meta-analysis of studies reported effect of intervention on adherence to anti-thrombotic drugs(23, 27). This analysis has also shown a significant effect of used interventions on adherence to anti-thrombotic drugs OR, 2.32; 95% CI (1.18, 4.56, [p=0.014]). Eight studies were excluded from this analysis; three were non-controlled(14, 20, 21), one used a matched group analysis(16) (unlike included studies), one did not record effect size of intervention on medication adherence(30) and two showed no change in adherence between groups(18, 25) (so no odds ratio could be calculated) and one(17) used the same population as(18) so was also excluded. Forest-plots were constructed for each analysis (figure 2).

Discussion

In this systematic review and meta-analysis we found that interventions that targeted risk factor control and encouraged self-care resulted in high continuation rate of secondary preventative medications after stroke. Interventions in six studies were shown to be potentially beneficial in maintaining higher continuation rate; many of which included an educational element which greatly influenced the importance of increasing patients' awareness regarding their prescribed medication.

A Cochrane review of interventions for risk factor control after stroke reported that educational or behavioural modification interventions were effective only as a part of a multi-approach intervention(33). Only one study in this Cochrane review that improved medication adherence was of behavioural change nature (cues, reminders and medication routine) combined with an educational element. This study was included in the current review(28). We found that both interventions used, definition of adherence and duration of follow-up varied considerably and that limited the validity of the benefit suggested by this review. The Cochrane review similarly reported huge heterogeneity of used interventions and reporting of outcomes and only produced a qualitative analysis with regards to adherence to secondary preventative medication.

Interventions that implemented change in practice, involved regimen modification or simplification, introduced environmental cues, or provided reminders or dosettes were usually effective in maintaining therapy with secondary preventative medications. Also, integrated care interventions that focused on risk factors management resulted in a high rate of adherence to secondary preventative medications after stroke. Another Cochrane review of interventions to improve medication adherence(34) reported that to be relatively efficient, interventions needed to be of a complex nature but effect was still modest.

In our narrative synthesis, we found that the majority of published studies suggested efficacy in improving adherence. This is an encouraging signal but in the absence of a formal meta-analysis we prefer not to interpret this finding as a definitive evidence of efficacy. We could only conclude that some interventions suggest a potential benefit and these were usually focused on increasing patients' awareness in addition to introducing behavioural change in order to enhance medication adherence. Given the shared features of these interventions, a further evaluation in larger samples would allow for more robust conclusion regarding which intervention would be most useful for patients with stroke.

Limitations

There were several limitations of this systematic review and meta-analysis. Data on interventions to enhance medication adherence after stroke was very limited and heterogeneous. Moreover, reporting of medication adherence is not universal (various scales, methodology e.g. subjective vs. objective) and studies that used questionnaires were not standardised and each used a different scale. Furthermore, different definitions of medication adherence were used and there was variable use of terminology e.g. adherence, compliance. In addition, there is no standardised scale to critically appraise type of included studies.

Strengths

This is the first systematic review to evaluate interventions used to enhance adherence to secondary prevention medication in stroke population. For the purpose of this systematic review and meta-analysis we identified a comprehensive list of synonyms and used multiple search engines. Also, we used a wide search strategy this is so we do not mistakenly exclude studies.

Implication for Practice

Additional focus should be given to stroke survivors as they are usually prescribed multiple

agents, some with frequent daily dosing in order to reach their target blood pressure levels.

Moreover, side effects can compromise adherence so if patients have such concerns, these

need to be clarified. This analysis has also reflected the crucial role of education on

medication changes at discharge on medication adherence.

Conclusion

Many interventions were simple and readily-available and were effective in maintaining

therapy with secondary preventative medications. Future research should focus on methods to

better prevent medication non-adherence.

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Disclosures

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Table 1: Characteristics of Intervention Studies						
Author	Population	Stroke Type	Follow w-up	Secondary preventative	Method to monitor adherence	Description of intervention
Douen 2008(14)	Intervention=130 Control=N/A	Any stroke eligible for Anti-platelet but not Anti-coagulant therapy	2 weeks	Aspirin Dipyridamole	Subjective-patient telephone interview	Dosage modification & follow-up at week 1 & 2
Evans-Hudnall 2014(22)	Intervention=30 Control=30	Any stroke	4 weeks	Not specified	Subjective-patient telephone interview	Secondary Stroke Prevention Program (STOP) = 3 stroke self-care & goal-setting activities at baseline & follow-up at 4 weeks
Hohmann 2013(23)	Intervention=155 Control=155	Any stroke	3 months	Anti-thrombotics Statins Overall regimen	Indirect-via Primary Care Physician	Education by clinical pharmacist at discharge
Hornnes 2011(24)	Intervention=172 Control=177	Any stroke	1 year	Anti-hypertensives	Subjective-patient interview	Motivational, educational & home visits
Ireland 2010(15)	Intervention=20 Control=from records of clinic (not specified quantity)	Minor stroke or TIA	6 months	Anti-hypertensives	Mixed: self-report, pill count & prescription renewal pattern	Motivational interviews & self-management approach to support behaviour change
Maasland 2007(25)	Intervention=33 Control=32	Minor stroke or TIA	3 months	Anti-platelets or Anti-coagulants Lipid-lowering medications Anti-hypertensives	Mixed-Monitoring BP and cholesterol levels and patient questionnaire	Educational, using multimedia computer program then assess patients awareness
MacKenzie 2013(26)	Intervention=29 Control=27	Any stroke	6 months	Not specified	Mixed-Self-report & prescription renewal patterns	Motivational interviews including counselling, regimen simplification,

						providing dosettes & monitoring BP
McManus 2009(27)	Intervention=49 Control=53	Any stroke	Mean of 3.6 years	Anti-platelets Anti-hypertensives Statins Overall regimen	Mixed: self-report & checking current medication with repeat prescriptions	Behaviour modification to improve risk factors management
Menard 2011(16)	Intervention=358 Control=participants in other studies	Any stroke	1 year	Anti-hypertensives Lipid-lowering drugs Anti-platelets or Anti-coagulants	Subjective-patient interview	Educational intervention aimed at risk factors reduction
O'Carroll 2013(28)	Intervention=31 Control=31	Any stroke	3 months	Anti-hypertensives Overall regimen	Mixed: electronic pill bottle & MARS scale	Environmental (introduced cues & modified beliefs regarding medication)
Ovbiagele 2005(17)	Intervention=144 Control=N/A	Ischaemic stroke or TIA	1 year	Anti-thrombotics Statins Anti-hypertensives	Subjective-patient telephone interview	The Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment (PROTECT) program
Ovbiagele 2004(18)	Intervention=130 Control=N/A	Ischaemic stroke or TIA	3 months	Anti-thrombotics Statins Anti-hypertensives	Subjective-patient telephone interview	PROTECT program
Sanossian 2006(19)	Intervention=92 Control=N/A	Ischaemic stroke or TIA	3 months	Statins	Mixed: Lab values of lipid profile and patients interview	Prescribing statin during hospitalisation
Sit 2007(29)	Intervention=77 Control=70	Minor stroke	3 months	Not specified	Subjective-Morisky compliance scale	Educational & motivational program to increase awareness and

						encourage self-care
Thrift 2014(20)	Intervention=256 Control=N/A	Any stroke but excluded subarachnoid haemorrhage	10 years	Anti-thrombotics Anti-hypertensives Statins	Subjective-patient interview	Initiating therapy and educating patients at discharge
Touze 2008(21)	Intervention=240 Control=N/A	Any stroke but excluded subarachnoid haemorrhage	1 year	Anti-thrombotics Overall regimen	Subjective-5-point Shea questionnaire	Initiating therapy while inpatient & close monitoring
Wolfe 2010(30)	Intervention=274 Control=249	Any stroke	12 – 18 months	Anti-hypertensives Anti-platelets Anti-coagulants Statins Diabetic medications	Subjective-patient interview	STOP stroke intervention, using "keeping well plan"

Table 2: Record of studies included in meta-analyses				
Study name	**Intervention**		**Control**	
	Effect size (%)	**N**	**Effect size (%)**	**N**
Overall secondary preventative drugs				
Evans-Hudnall 2014	25 (93)	27	15 (60)	25
Hohmann 2013	133 (91)	146	112 (83)	135
McManus 2009	29 (78)	37	36 (92)	39
O'Carroll 2013	29 (99)	29	27 (94)	29
Blood pressure lowering drugs				
Hornnes 2011	96 (98)	98	110 (99)	111
Ireland 2010	17 (85)	20	16 (80)	20
Maasland 2007	28 (92)	30	25 (92)	27
McManus 2009	36 (97)	37	41 (95)	43
Menard 2011	278 (78)	358	221 (62)	358
Ovbiagele 2004	109 (84)	130	122 (94)	130
Lipid-lowering drugs				
Hohmann 2013	121 (88)	138	90 (70)	129
Maasland 2007	28 (93)	30	25 (93)	27
McManus 2009	32 (88)	36	39 (89)	44
Anti-thrombotic drugs				
Hohmann 2013	137 (92)	149	119 (84)	142
McManus 2009	44 (96)	46	44 (88)	50
N: total number of subjects				

List of figures:

Figure 1: PRISMA Flow Diagram

Figure 2: Forest plots of meta-analyses of intervention studies to enhance adherence to secondary preventative medication after stroke
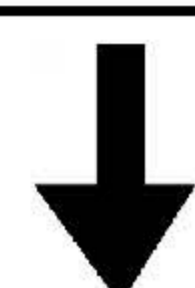
Bibliographic databases searched
Ovid Medline (1946 – April 2014)
Ovid Embase (1947 – April 2014)
Web of knowledge (Thomson Reuters)
CENTRAL (Cochrane)
CINAHL (EBSCOhost)
PsycINFO (EBSCOhost)

Concept 1: Stroke/ TIA

Concept 2: Medication Adherence

Search combined Concept 1 & Concept 2 terms

Total titles reviewed = 12,237

Total abstracts checked = 143

Reasons for exclusion
Guidelines adherence by practitioners (13)
Non-stroke patients (13)
Not quantified adherence (9)
Primary prevention (3)
Non-pharmacological (6)
Service evaluation (6)
Management in acute phase (1)
Conference abstract (21)
Protocols or reviews (14)
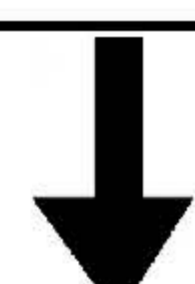
Full papers screened = 57

Reasons for exclusion
Non-interventional studies:
Observational (27)
Epidemiological (13)

Included in Systematic Review = 17

Included in Meta-analysis:

Overall regimen = 4
(3 excluded; 2 used different scales & 1 uncontrolled)

Blood-pressure lowering drugs = 6
(4 excluded; 1 uncontrolled, 1 used scale result, 1 not recorded effect size,
1 used duplicate population)

Lipid-lowering drugs = 3
(7 excluded; 2 uncontrolled, 2 had no effect size recorded, 2 used matched
group analysis, 1 used duplicate population)

Anti-thrombotic drugs = 2
(8 excluded; 3 uncontrolled, 1 used matched-group analysis, 1 did not record
effect size, 2 had no change between groups, 1 used duplicate population)

Meta-Analysis: Effect of Intervention on Adherence to Overall Regimen

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Odds ratio and 95% CI
		Statistics for each study				
Evans-Hudnall 2014 All	8.333	1.604	43.288	2.522	0.012	
Hohmann 2013 All	2.101	1.017	4.338	2.007	0.045	
McManus 2009 All	0.302	0.073	1.242	-1.659	0.097	
O'Carroll 2013 All	5.364	0.246	116.761	1.069	0.285	
	1.964	0.503	7.671	0.971	0.332	

0.01　0.1　1　10　100

Favours Control　　Favours Intervention
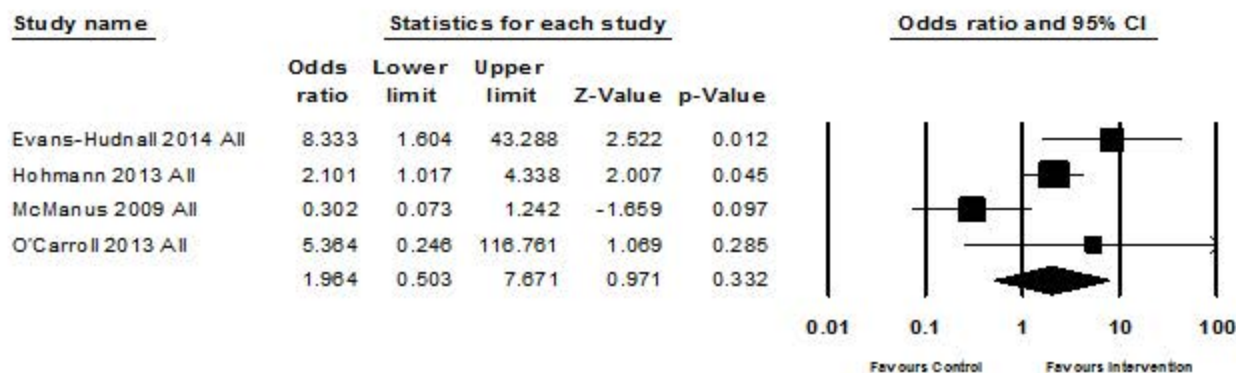
Q-value= 10.091, P-value= 0.018, I-squared= 70.271

Meta-Analysis: Effect of Intervention on Adherence to Blood Pressure-lowering Medication

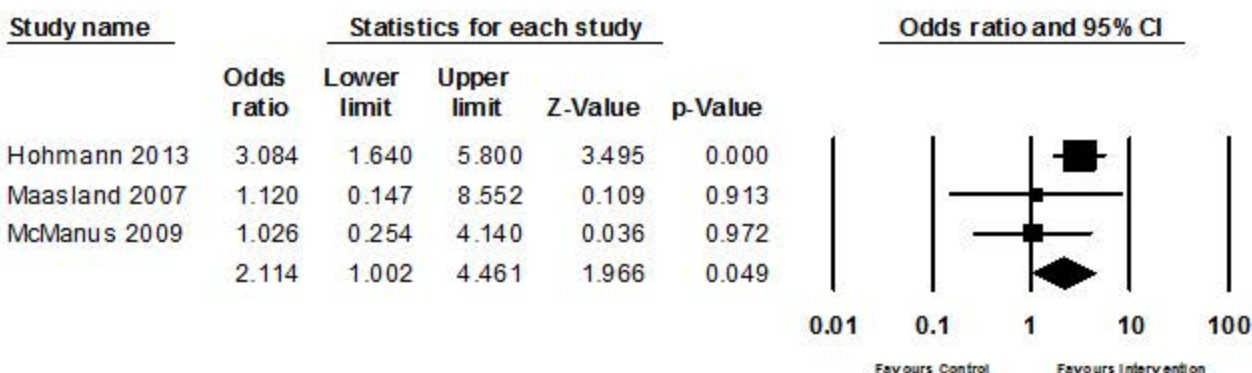| Group by Subgroup within study	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Odds ratio and 95% CI
				Statistics for each study				
Matched	Ireland 2010	Matched	1.417	0.273	7.342	0.415	0.678	
Matched	Menard 2011	Matched	2.154	1.553	2.989	4.593	0.000	
Matched	Oviasgie 2004	Matched	2.938	1.250	6.904	2.473	0.013	
Matched			2.207	1.634	2.982	5.162	0.000	
Unmatched	Homnes 2011	Unmatched	0.436	0.039	4.888	-0.673	0.501	
Unmatched	Maasland 2007	Unmatched	1.120	0.147	8.552	0.109	0.913	
Unmatched	McManus 2009	Unmatched	1.756	0.153	20.185	0.452	0.651	
Unmatched			0.966	0.260	3.586	-0.052	0.959	

0.01　0.1　1　10　100

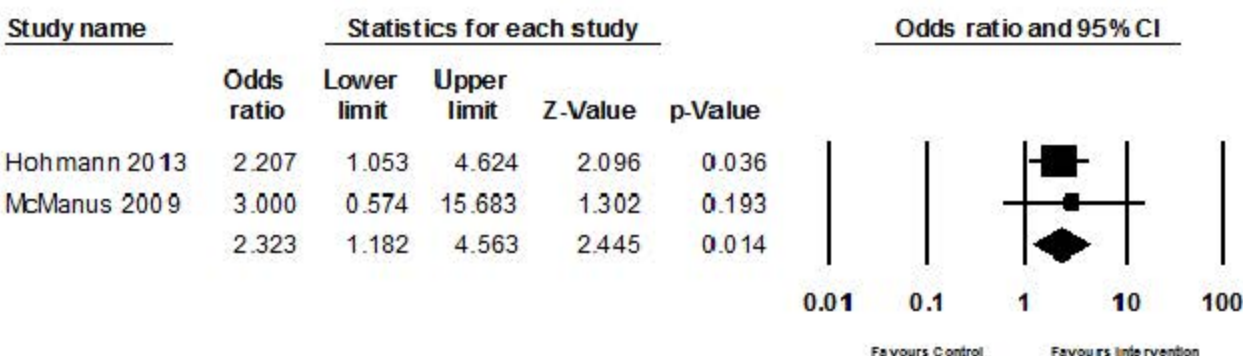Favours Control　　Favours Intervention

Matched: Q=0.731, P= 0.694, I-squared= 0.000; Unmatched: Q=0.666, P= 0.717, I-squared= 0.000

Meta-Analysis: Effect of Intervention on Adherence to Lipid-lowering Medication

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Odds ratio and 95% CI
		Statistics for each study				
Hohmann 2013	3.084	1.640	5.800	3.495	0.000	
Maasland 2007	1.120	0.147	8.552	0.109	0.913	
McManus 2009	1.026	0.254	4.140	0.036	0.972	
	2.114	1.002	4.461	1.966	0.049	

0.01　0.1　1　10　100

Favours Control　　Favours Intervention

Q-value=2.572, P-value= 0.276, I-squared= 22.233

Meta-Analysis: Effect of Intervention on Adherence to Anti-thrombotics

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Odds ratio and 95% CI
		Statistics for each study				
Hohmann 2013	2.207	1.053	4.624	2.096	0.036	
McManus 2009	3.000	0.574	15.683	1.302	0.193	
	2.323	1.182	4.563	2.445	0.014	

0.01　0.1　1　10　100

Favours Control　　Favours Intervention

Q-value= 0.110, P-value= 0.740, I-squared= 0.000