

# BMJ Open Enhancing prescribing of guideline-recommended medications for ischaemic heart diseases: a systematic review and meta-analysis of interventions targeted at healthcare professionals

Thang Nguyen,<sup>1,2</sup> Hoa Q Nguyen,<sup>3</sup> Niken N Widyakusuma,<sup>4</sup> Thao H Nguyen,<sup>3</sup> Tam T Pham,<sup>5</sup> Katja Taxis<sup>2</sup>

**To cite:** Nguyen T, Nguyen HQ, Widyakusuma NN, *et al*. Enhancing prescribing of guideline-recommended medications for ischaemic heart diseases: a systematic review and meta-analysis of interventions targeted at healthcare professionals. *BMJ Open* 2018;**8**:e018271. doi:10.1136/bmjopen-2017-018271

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-018271>).

Received 15 June 2017

Revised 1 November 2017

Accepted 10 November 2017



CrossMark

For numbered affiliations see end of article.

## Correspondence to

Thang Nguyen;  
ngthang85@yahoo.com

## ABSTRACT

**Objectives** Ischaemic heart diseases (IHDs) are a leading cause of death worldwide. Although prescribing according to guidelines improves health outcomes, it remains suboptimal. We determined whether interventions targeted at healthcare professionals are effective to enhance prescribing and health outcomes in patients with IHDs.

**Methods** We systematically searched PubMed and EMBASE for studies published between 1 January 2000 and 31 August 2017. We included original studies of interventions targeted at healthcare professionals to enhance prescribing guideline-recommended medications for IHDs. We only included randomised controlled trials (RCTs). Main outcomes were the proportion of eligible patients receiving guideline-recommended medications, the proportion of patients achieving target blood pressure and target low-density lipoprotein-cholesterol (LDL-C)/cholesterol level and mortality rate. Meta-analyses were performed using the inverse-variance method and the random effects model. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation approach.

**Results** We included 13 studies, 4 RCTs (1869 patients) and 9 cluster RCTs (15224 patients). 11 out of 13 studies were performed in North America and Europe. Interventions were of organisational or professional nature. The interventions significantly enhanced prescribing of statins/lipid-lowering agents (OR 1.23; 95% CI 1.07 to 1.42, P=0.004), but not other medications (aspirin/antiplatelet agents, beta-blockers, ACE inhibitors/angiotensin II receptor blockers and the composite of medications). There was no significant association between the interventions and improved health outcomes (target LDL-C and mortality) except for target blood pressure (OR 1.46; 95% CI 1.11 to 1.93; P=0.008). The evidence was of moderate or high quality for all outcomes.

**Conclusions** Organisational and professional interventions improved prescribing of statins/lipid-lowering agents and target blood pressure in patients with IHDs but there was little evidence of change in other outcomes.

**PROSPERO registration number** CRD42016039188.

## Strengths and limitations of this study

- This is a systematic review and meta-analysis of randomised controlled trials, conducted following the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.
- This review focused on interventions targeted at healthcare professionals to enhance prescribing of individual medications for acute coronary syndrome. Interventions were classified according to the Cochrane Effective Practice and Organization of Care Review Group. But more detailed analyses, for example, on duration or intensity of intervention implementation, were impossible due to the limited number of studies.
- We may have missed relevant unpublished or locally published studies as we restricted our search to English publications and did not search for grey literature.

## INTRODUCTION

Ischaemic heart diseases (IHDs) are a leading cause of death worldwide accounting for 13.2% of all deaths globally.<sup>1</sup> IHDs include angina pectoris and myocardial infarction.<sup>2</sup> International guidelines recommend using a combination of an antiplatelet agent, a beta-blocker, an ACE inhibitor or an angiotensin II receptor blocker (ACEI/ARB) and an HMG coenzyme A reductase inhibitor (statin) to treat eligible patients with IHDs.<sup>3–8</sup> This combination is an effective secondary prevention after myocardial infarction, reducing morbidity and mortality.<sup>9–13</sup> Despite such evidence, rates of patients being prescribed medications according to guidelines varied from <5.0% to >95.0%,

leaving a substantial proportion of patients with IHDs not receiving guideline-recommended care.<sup>14–17</sup> Changing clinicians' behaviour to improve prescribing guideline-recommended medications is challenging. Different types of interventions have been developed and classified as professional interventions (eg, education,<sup>18–21</sup> reminders,<sup>22</sup> audit and feedback<sup>23</sup>), organisational interventions (eg, computerised clinical guidelines,<sup>24</sup> pharmacist-led intervention<sup>25</sup>), financial interventions (eg, financial incentives<sup>26</sup>) and regulatory interventions (eg, cap and copayment policies<sup>27</sup>).

Interventions to improve prescribing guideline-recommended medications for cardiovascular diseases, in general, have been reviewed recently.<sup>28–29</sup> Moreover, Murphy *et al* have evaluated the effect of organisational interventions for patients with IHDs.<sup>30</sup> The interventions aimed to improve mortality and hospital admissions and targeted physicians and patients to adhere to recommendations of secondary prevention of IHDs (lifestyle modification, prescribing medications or both).<sup>30</sup> No work has been done synthesising the evidence on interventions to enhance prescribing according to guidelines for patients with IHDs as far as we are aware. In this review, we focus on interventions targeted at health professionals. Other factors influencing prescribing, such as patient behaviour, organisational factors or resource constraints are outside the scope of this review.<sup>31</sup> We conducted a systematic review and meta-analysis to determine whether interventions targeted at healthcare professionals are effective to enhance prescribing and health outcomes in patients with IHDs.

## METHODS

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement<sup>32</sup> and the Cochrane Handbook for Systematic Reviews of Interventions.<sup>33</sup> We registered our protocol with the International Prospective Register of Systematic Reviews Registry (CRD42016039188).<sup>34</sup>

We searched the electronic bibliographic databases PubMed and EMBASE as these are considered to be the most important sources for reports of trials.<sup>33</sup> The search strategy included MeSH terms and relevant keywords in various combinations relating to guidelines, guideline adherence, drug therapy, IHDs and randomised trials (see online supplementary appendix A). We restricted our search to studies carried out in humans and published in English. Studies published between 1 January 2000 and 31 August 2017 were sought. References of included articles were manually screened to identify additional eligible studies.

We included original studies reporting results of randomised controlled trials (RCTs) or cluster randomised controlled trials (cluster RCTs) in patients with IHDs eligible for receiving secondary preventive treatment. Studies had to evaluate interventions targeted

at healthcare professionals to enhance prescribing of guideline-recommended medications. The trials had to include at least one prospectively assigned concurrent control group. The control group had to receive usual care (not receiving the intervention), or an intervention of lower intensity or shorter duration than the intervention group. Studies had to report patient-level outcomes. We excluded duplicate reports, post hoc analyses or abstracts from meeting proceedings unless published as full-text reports in a peer-reviewed journal. We excluded studies on patients receiving acute treatment in hospital only; or interventions predominantly targeting patient medication-taking behaviour or lifestyle modifications.

All titles and abstracts retrieved from the electronic searches were archived in the web-based bibliography and database manager RefWorks. After removing duplicates, two reviewers (TN and HQN) independently screened the titles and abstracts. They also independently assessed the full text of potentially eligible studies. Disagreements between the reviewers whether to include or exclude a study were resolved by consensus.

Two reviewers (TN and NNW) independently extracted data from the trials' primary texts, the online supplementary appendices and protocols using a data abstraction form. We extracted the following information: trial name, year of publication, sources of funding, setting and time of recruitment, study design, study population characteristics, details of the intervention and control conditions, main outcomes and evidence for assessment of the risk of bias. Disagreements were resolved by discussion with a third reviewer (KT).

Two reviewers (TN and NNW) independently assessed the risk of bias of each study using the tool of the Cochrane Effective Practice and Organization of Care Review Group (EPOC).<sup>35</sup> The nine standard criteria were: (1) random sequence generation, (2) allocation sequence concealment, (3) similarity of baseline outcome measures, (4) similarity of baseline characteristics, (5) blinding of outcome assessment, (6) adequately addressing incomplete outcome data, (7) adequate protection against contamination, (8) free from selective reporting and (9) free from other risks of bias (eg, recruitment bias or not adjusting for clustering effect in cluster RCTs).<sup>35</sup> Disagreements were resolved by discussion with a third reviewer (KT). We judged trials with four or more high-risk domains, or three or more high-risk domains plus three or more unknown domains as having a high risk of bias.

The primary outcomes were the proportion of eligible patients receiving the following guideline-recommended medications: aspirin/antiplatelet agents, beta-blockers, ACEIs/ARBs, statins/lipid-lowering agents and a composite of these medications. The secondary outcomes were: the proportion of eligible patients achieving target blood pressure and target LDL-C/cholesterol level, and the mortality rate.

The interventions were classified according to the taxonomy of the EPOC<sup>36</sup> as professional, financial,

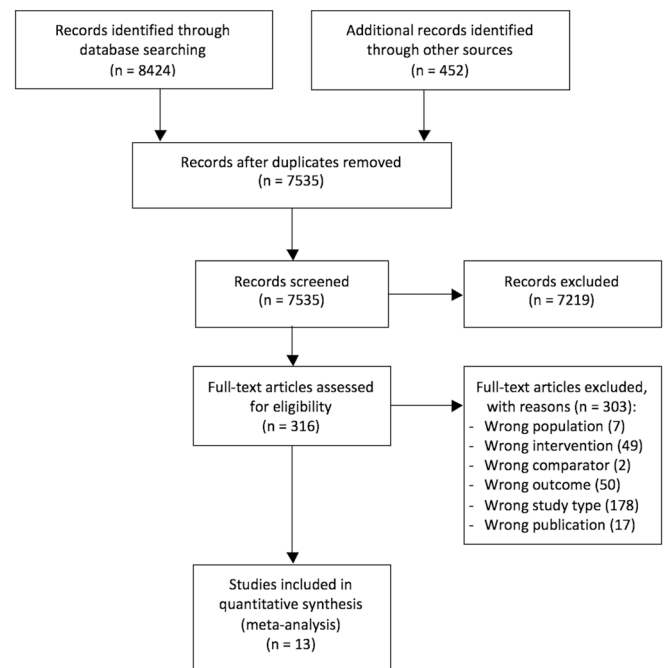
organisational or regulatory interventions. We performed meta-analyses for outcomes when the necessary data were available. Meta-analyses were performed in the Review Manager V.5.3 (RevMan 5)<sup>37</sup> using the inverse-variance method and the random effects model. The main outcomes were measured as dichotomous variables. The OR with corresponding 95% CI was calculated for each outcome of interest to generate a forest plot. For studies with more than two trial groups, we combined relevant groups to create a single pair-wise comparison.<sup>33</sup> A Z-test was used to assess the statistical significance of the results of the meta-analysis with a two-tailed P value of <0.05. The intracluster correlation coefficients (ICCs) for cluster RCTs were used to calculate the effective sample size to ensure the clustering effect was taken into account in our analyses. When an ICC was not reported in a cluster RCT, we contacted the trial authors. In case of non-response, we used the mean of corresponding ICCs reported in the other included cluster RCTs to adjust for the clustering effect.<sup>38 39</sup>

Two reviewers (KT and TN) independently assessed the quality of evidence across included studies of all outcomes of interest using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.<sup>40</sup> The following criteria were used: serious limitations in study design and implementation, indirectness, substantial heterogeneity, imprecision and publication bias. The GRADE approach specifies four levels of quality: high, moderate, low and very low. The quality rating was downgraded by one level for each factor having a serious limitation, up to a maximum of three levels for all factors. Heterogeneity across trials for each outcome of interest was investigated using the Cochran's Q test and was measured by the I<sup>2</sup> statistic. An I<sup>2</sup> exceeding 50% indicated substantial statistical heterogeneity.<sup>33 41</sup> Publication bias was evaluated visually by inspecting funnel plots and quantified by the Egger's test for outcomes comprising at least 10 trials.<sup>33 42</sup>

We performed subgroup analyses and sensitivity analyses when the necessary data were available. Subgroup analyses were performed for type of study designs, type of intervention, comparators and setting of the intervention. We examined the robustness of our findings in sensitivity analyses excluding studies with high overall risk of bias, and analyses without adjusting for clustering effect.<sup>33</sup>

## RESULTS

The search of PubMed and EMBASE databases provided a total of 8424 citations, and 452 citations were added from the lists of references from included studies. After removing duplicates, 7535 remained. Of those, 7219 papers were discarded after screening titles and abstracts. The full text of 316 studies was examined in more detail, 303 studies did not meet the inclusion criteria. A total of 13 studies<sup>43-59</sup> were identified for inclusion in the review (figure 1). These were 4 RCTs<sup>45 49 51 59</sup> involving 1869 patients and 9 cluster RCTs<sup>43 47 50 52 53 55-58</sup> involving 599



**Figure 1** Flow chart diagram of study selection.

healthcare centres and 15 224 patients. Trials were carried out between 1997 and 2012 and published between 2001 and 2015. Control groups received usual care (nine studies<sup>43 45 49-52 55 58 59</sup>) or less intensive interventions (four studies<sup>47 53 56 57</sup>). Seven studies<sup>43 49 52 53 55 57 59</sup> reported patients' health outcomes (table 1). The overall risk of bias was rated as low in all included studies (table 1 and more details in online supplementary appendix B).

Five studies<sup>45 49 50 52 59</sup> used organisational interventions, four studies<sup>51 53 55 58</sup> professional interventions and four studies<sup>43 47 56 57</sup> a combination of organisational and professional interventions. Distribution of educational materials, educational outreach visits, audit and feedback and reminders were the four professional interventions most frequently used. Continuity of care, communication and case discussions between distant healthcare professionals were the two organisational interventions most frequently used (table 2 and more details in online supplementary appendix C).

Interventions had no significant effect on prescribing guideline-recommended medications, that is, there was no significant difference in the proportion of eligible patients receiving guideline-recommended medications between intervention and control groups except for statins/lipid-lowering agents. The findings were aspirin/antiplatelet agents (OR 1.13; 95% CI 0.87 to 1.47; P=0.360), beta-blockers (OR 1.13; 95% CI 0.93 to 1.37; P=0.230), ACEIs/ARBs (OR 1.04; 95% CI 0.88 to 1.23; P=0.620) and statins/lipid-lowering agents (OR 1.23; 95% CI 1.07 to 1.42; P=0.004), the composite of medications (OR 1.07; 95% CI 0.73 to 1.58; P=0.720). The evidence was of moderate or high quality for the primary outcomes (figure 2 and table 3).

**Table 1** Characteristics of included studies

No. Source	Study design	Study period	Patient follow-up, months	Country	Setting of recruitment	Diagnosis	Intervention group			Control group			Primary outcome	Secondary outcome	Overall risk of bias		
							Type	No. of patients (clusters)	Age, mean (SD)	Gender, % male	Type	No. of patients (clusters)				Age, mean (SD)	Gender, % male
1 Berwanger et al <sup>43</sup>	Cluster RCT	2011–2012	1	Brazil	Hospital	ACS	OI plus PI	602 (17)	62 (13)	68.6	UC	548 (17)	62 (13)	68.6	ASA, BB, ACEI, statin, composite	30-day mortality	Low
2 Bond et al <sup>45</sup>	RCT	2002–2004	12	UK	GP/PCP	IHD	OI	941	68.7 (9.2)	67.4	UC	500	68.8 (9.1)	70.6	ASA, BB, ACEI, LLA	No	Low
3 Flather et al <sup>47</sup>	Cluster RCT	2008	NA	France, Italy, Poland, Spain, UK	Hospital	NSTEMACS	OI plus PI	722 (19)	65.6 (10.5)	67.2	LII	479 (18)	66.1 (10.6)	72.2	CLO, BB, ACEI, statin	No	Low
4 Garcia et al <sup>49</sup>	RCT	2009–2010	12	Norway	Hospital	IHD	OI	48	63.9 (9)	72	UC	46	63.4 (9.9)	72	ASA, BB, ACEI/ARB, statin	Target BP, target LDL-C	Low
5 Guadagnoli et al <sup>50</sup>	Cluster RCT	1999–2001	6	USA	Hospital	MI	OI	232 (184)	68.3 (11.3)	66.4	UC	227 (210)	67.3 (12.1)	63.9	ASA, BB and ACEI	No	Low
6 Hung et al <sup>51</sup>	RCT	2004–2007	6	Taiwan	Hospital	IHD	PI	92	67 (10)	71.7	UC	102	66 (12)	75.2	LLA	No	Low
7 Khuntia et al <sup>52</sup>	Cluster RCT	2001–2003	12	UK	GP/PCP	IHD	OI	461 (10)	Median (IQR) 70 (63, 76)	69	UC	619 (10)	Median (IQR) 71 (63, 78)	60	ASA, BB, ACEI, LLA	Target BP, target cholesterol	Low
8 Levine et al <sup>53</sup>	Cluster RCT	2002–2008	27	USA	GP/PCP	post-MI	PI	3080 (84)	<65: 48.5%; ≥65: 51.5%	98.8	LII	2911 (84)	<65: 46.9%; ≥65: 53.1%	98.7	BB, ACEI/ARB, statin	Target LDL-C	Low
9 McAlister et al <sup>55</sup>	Cluster RCT	2005–2008	6	Canada	GP/PCP	IHD	PI	165 (NR) 158 (NR)	64.5 (10.2) 62.9 (9.7)	72.1 81.7	UC	157 (NR)	64.4 (9.6)	82.1	APA, BB, ACEI/ARB, statin, composite	Target LDL-C, 6 month mortality	Low
10 Moher et al <sup>56</sup>	Cluster RCT	1997–1999	18	UK	GP/PCP	IHD	OI plus PI	682 (7) 665 (7)	66.4 (5.6) 65.8 (5.8)	67 71	LII	559 (7)	66.1 (5.4)	67	APA, LLA	No	Low
11 Ornstein et al <sup>57</sup>	Cluster RCT	2002–2003	24	USA	GP/PCP	IHD	OI plus PI	1422 (10)	NR	NR	LII	1166 (10)	NR	NR	BB, LLA	Target BP, target LDL-C	Low
12 Sondergaard et al <sup>58</sup>	Cluster RCT	2000–2002	NA	Denmark	GP/PCP	IHD	PI	157 (14)	NR	NR	UC	162 (14)	NR	NR	ASA, LLA	No	Low
13 Yorio et al <sup>59</sup>	RCT	2003–2004	12	USA	Hospital	ACS	OI	72	55.9 (11.3)	66.7	UC	68	56.2 (10.8)	57.3	ASA, BB, ACEI, statin	Target SBP, target LDL-C	Low

ACEI, ACE inhibitors; ACS, acute coronary syndrome; APA, antiplatelet agents; ARB, angiotensin II receptor blockers; ASA, aspirin; BB, beta-blockers; BP, blood pressure; CLO, clopidogrel; GP, general practice; IHD, ischaemic heart disease; LDL-C, low-density lipoprotein cholesterol; LII, less intensive intervention; LLA, lipid-lowering agents; MI, myocardial infarction; NA, not applicable; NR, not reported; NSTEMACS, non-ST-elevation acute coronary syndrome; OI, organisational intervention; PCP, primary care practice; PI, professional intervention; RCT, randomised controlled trials; SBP, systolic blood pressure; UC, usual care.

**Table 2** Intervention description

		Intervention description												
		Professional intervention*						Organisational intervention*						
No.	Source	Setting of intervention implementation	Intervention carried out by	Distribution of educational materials	Educational meeting	Educational outreach visits	Local opinion leaders	Audit and feedback	Reminders	Revision of professional roles	Clinical multidisciplinary teams	Continuity of care	Communication and case discussion between distant healthcare professionals	Presence and organisation of quality monitoring mechanisms
1	Berwanger <i>et al</i> <sup>43</sup>	Hospital	Nurse and physician	x	x	x		x				x		
2	Bond <i>et al</i> <sup>45</sup>	Pharmacy	Community pharmacist									x	x	
3	Flather <i>et al</i> <sup>47</sup>	Hospital	Cardiologist, nurse and manager		x	x		x			x			x
4	Garcia <i>et al</i> <sup>49</sup>	GP/PCP	Hospital pharmacist										x	
5	Guadagnoli <i>et al</i> <sup>50</sup>	GP/PCP	Cardiologist										x	
6	Hung <i>et al</i> <sup>51</sup>	Hospital	Reminder system						x					
7	Khunti <i>et al</i> <sup>52</sup>	GP/PCP	Nurse							x		x	x	
8	Levine <i>et al</i> <sup>53</sup>	GP/PCP	Internet-delivered intervention system	x										
9	McAllister <i>et al</i> <sup>55</sup>	GP/PCP	Leader				x							
10	Moher <i>et al</i> <sup>56</sup>	GP/PCP	General practitioner and nurse					x	x					
11	Ornstein <i>et al</i> <sup>57</sup>	GP/PCP	Not specified	x	x	x		x	x					x
12	Sondergaard <i>et al</i> <sup>58</sup>	GP/PCP	Not specified	x	x	x		x						
13	Yorio <i>et al</i> <sup>59</sup>	Cardiology clinic	Nurse or clinical pharmacist									x		

\*The interventions were classified according to the taxonomy of the Cochrane Effective Practice and Organization of Care Review Group. GP, general practice; PCP, primary care practice.

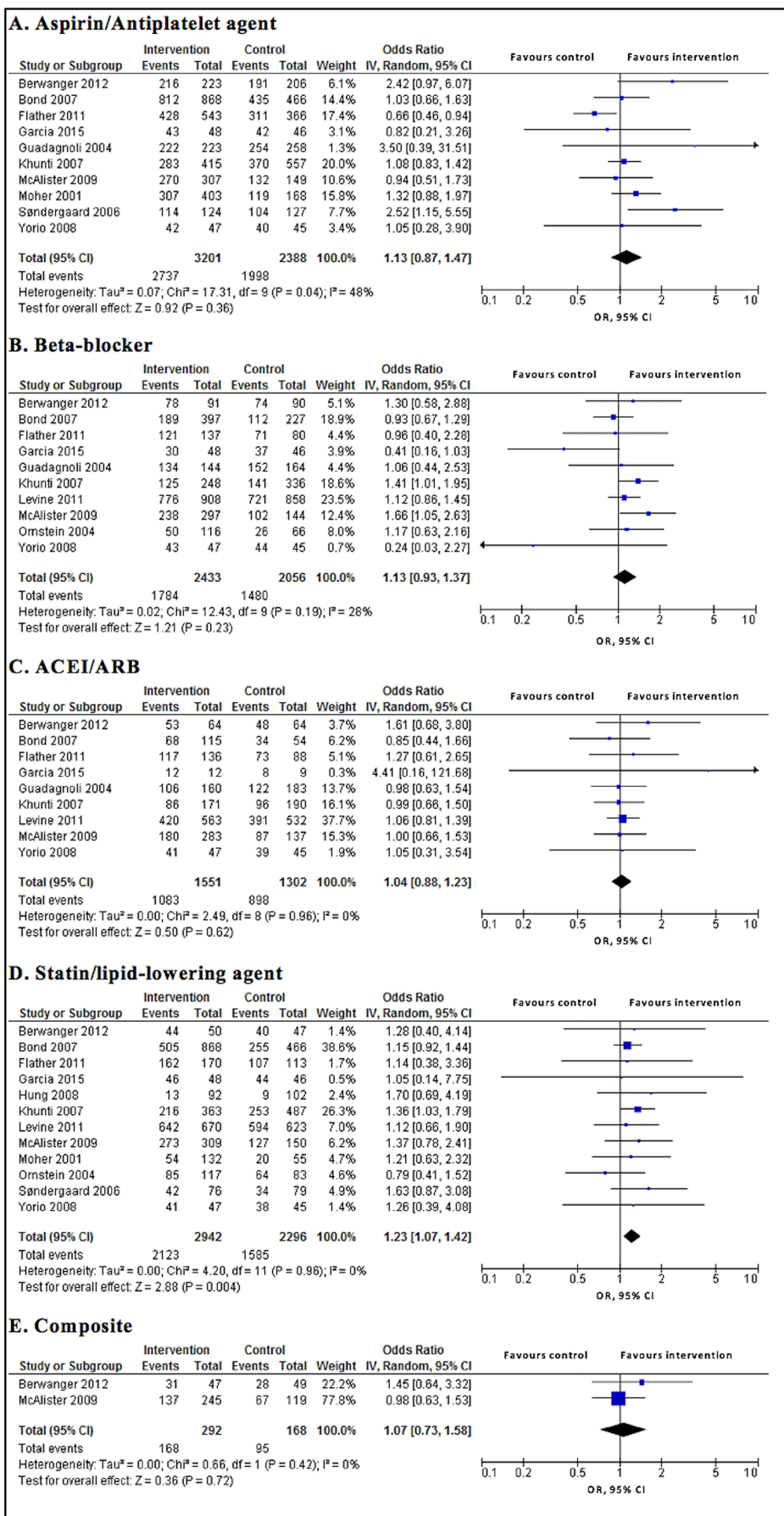


Figure 2 Primary outcomes of intervention vs control. ACEI, ACE inhibitors; ARB, angiotensin II receptor blocker.

**Table 3** Summary of findings and quality assessment

Outcome	Quality assessment (serious limitation, yes/no/unknown)				Summary of findings				Quality of the evidence (GRADE)	
	Study design	Indirectness	Substantial statistical heterogeneity	Imprecision	Publication bias	Illustrative comparative risks (95% CI)		Relative effect, OR (95% CI)		No. of patients (studies)
						Assumed risk in comparison	Corresponding risk in intervention			
ASA/APA	Yes*	No	No	No	No	851 per 1000	866 per 1000 (832 to 894)	1.13 (0.87 to 1.47)	5589 (10 studies)	Moderate
BB	Yes*	No	No	No	No	840 per 1000	856 per 1000 (830 to 878)	1.13 (0.93 to 1.37)	4489 (10 studies)	Moderate
ACEI/ARB	No	No	No	No	Unknown†	735 per 1000	743 per 1000 (709 to 773)	1.04 (0.88 to 1.23)	2853 (9 studies)	High
Statin/LLA	Yes*	No	No	No	No	770 per 1000‡	805 per 1000 (782 to 826)	1.23 (1.07 to 1.42)	5238 (12 studies)	Moderate
Composite	No	No	No	No	Unknown†	566 per 1000	583 per 1000 (488 to 673)	1.07 (0.73 to 1.58)	460 (2 studies)	High
Target BP	Yes*	No	No	No	Unknown†	432 per 1000	526 per 1000 (458 to 595)	1.46 (1.11 to 1.93)	1580 (4 studies)	Moderate
Target LDL-C/cholesterol	Yes*	No	No	No	Unknown†	704 per 1000	714 per 1000 (682 to 744)	1.05 (0.90 to 1.22)	3194 (6 studies)	Moderate
Mortality	No	No	No	Yes§	Unknown†	84 per 1000	67 per 1000 (42 to 104)	0.78 (0.48 to 1.27)	1341 (2 studies)	Moderate

Patient or population: patients with ischaemic heart diseases.

Comparison: usual care or less intensive intervention.

Intervention: interventions intended to improve prescribing guideline-recommended medications and patients' health outcomes.

§Included study had few events and wide CI.

\*More than one-third of studies had recruitment bias.

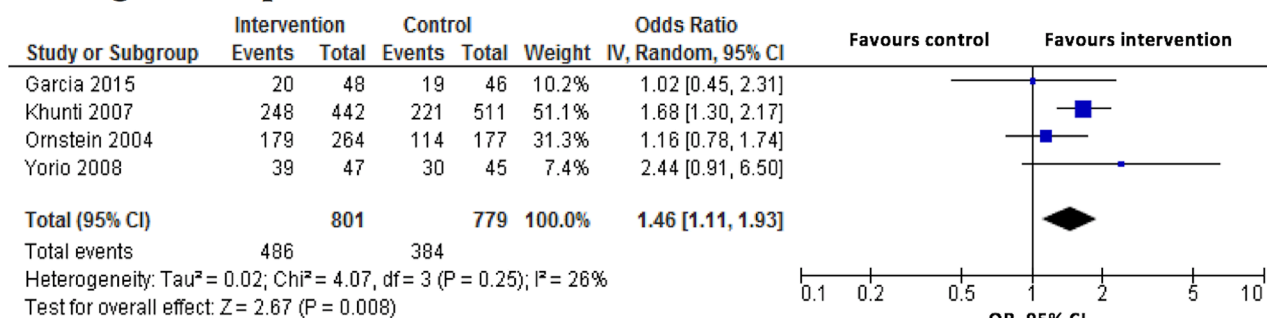
†Did not perform Egger's test because of number of studies <10.

‡Not included the study by Hung *et al* because its population was the patients not receiving statin/LLA appropriately at baseline.

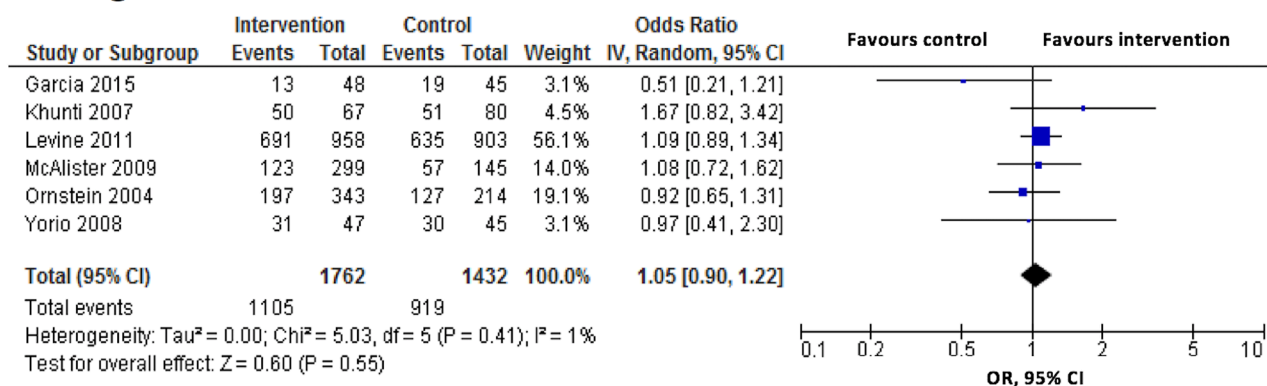
Setting: hospitals, general practices/primary care practices, cardiology clinics or pharmacies.

ACEI, ACE inhibitors; APA, antiplatelet agents; ARB, angiotensin II receptor blockers; ASA, aspirin; BB, beta-blockers; BP, blood pressure; GRADE, grading of recommendations assessment, development and evaluation; LDL-C, low-density lipoprotein cholesterol; LLA, lipid-lowering agents.

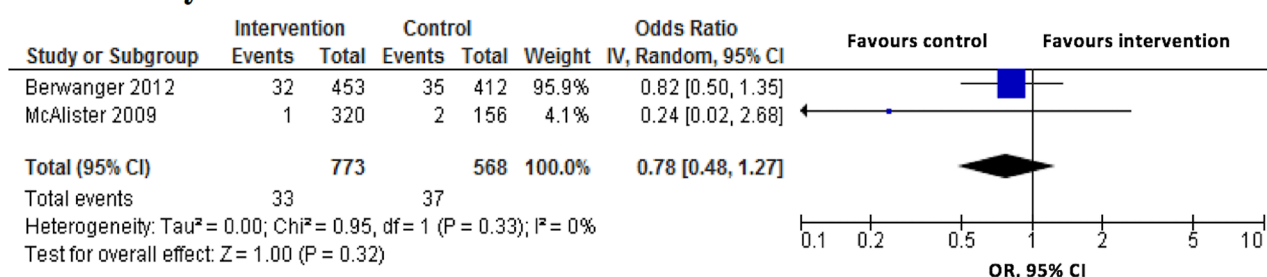
## A. Target blood pressure



## B. Target LDL-C/cholesterol



## C. Mortality



**Figure 3** Secondary outcomes of intervention vs control. LDL-C, low-density lipoprotein-cholesterol.

The interventions significantly increased the proportion of patients achieving target blood pressure (OR 1.46; 95% CI 1.11 to 1.93;  $P=0.008$ ), but there was no significant difference in the proportion of patients achieving target LDL-C/cholesterol (OR 1.05; 95% CI 0.90 to 1.22;  $P=0.550$ ), and in mortality rate (OR 0.78; 95% CI 0.48 to 1.27;  $P=0.320$ ) between intervention and control groups. The evidence was of moderate quality for the secondary outcomes (figure 3 and table 3).

No substantial statistical heterogeneity was detected in our study outcomes (all eight  $I^2$  values were  $<50\%$ ) (figure 2 and figure 3). The publication bias was rated as no risk (in aspirin/antiplatelet agents, beta-blockers and statins/lipid-lowering agents) and unknown risk (in the other outcomes) (see online supplementary appendix D). In subgroup analyses, there was no significant difference in the effect of the interventions on prescribing

guideline-recommended medications and patients' health outcomes between subgroups with all  $P$  values for the interaction of  $>0.05$ . No subgroup analysis could be done for the composite of medications and mortality rate as there were only two studies available for each of these outcomes (see online supplementary appendix E). We did not perform sensitivity analyses excluding studies with high overall risk of bias because all included studies were rated as low risk. The findings of all outcomes did not change in sensitivity analyses when not adjusting for clustering effects (see online supplementary appendix F).

## DISCUSSION

Interventions to enhance prescribing guideline-recommended medications for patients with IHDs were of organisational or professional nature. The interventions



significantly enhanced prescribing of statins/lipid-lowering agents, but not other medications. There was no significant association between the interventions and improved health outcomes, except for target blood pressure. The evidence was of moderate or high quality for all outcomes.

Why did the interventions not improve prescribing of most medications? The high baseline performance, especially of antiplatelet agents, might limit the scope for further improvement.<sup>45 47 49 50 53 59</sup> The baseline measures were better than expected which may indicate 'a rising tide phenomenon', a metaphor for a secular upward trend, being a possible explanation of null results.<sup>60</sup> In addition, an increased awareness of treatment recommendations derived from efforts by local organisations and reports documenting poor compliance with recommendations could contribute to this phenomenon.<sup>50 60</sup> The Hawthorne effect may also explain the results. Extra attention by researchers and higher levels of clinical surveillance, equally present in treatment and control groups, may over-estimate response in both groups.<sup>61</sup> As a consequence, the control groups improved their performance alongside the intervention groups in included studies.<sup>52 53 55-58</sup> Furthermore, many other factors impact on prescribing including patients and resource constraints which were not assessed in the studies.<sup>31</sup>

What are possible explanations for finding effects on prescribing statins/lipid-lowering agents? First, there were more patients eligible for receiving statins/lipid-lowering agents than antihypertensive agents (beta-blockers or ACEIs/ARBs). Furthermore, statins/lipid-lowering agents are recommended to be prescribed for all patients with IHDs, regardless of their LDL-C level.<sup>3-8</sup> Physicians tend to be more careful when prescribing beta-blockers because of concerns about their side effects.<sup>62</sup> Physicians also possibly favoured other classes of medications to monitor patients' blood pressure level and survival (eg, calcium channel inhibitors).<sup>62</sup> It was surprising that the interventions had an impact on prescribing of statins/lipid-lowering agents, but not on LDL-C/cholesterol level. In contrast, interventions did not have an impact on prescribing antihypertensive agents, but target blood pressure improved. Whether or not adequate dosing had been achieved was not measured in the trials, but this has an effect on patients' outcomes. For example, the benefits of more intensive therapy with statins have been established.<sup>63</sup> Lack of patient adherence with medication could also be an explanation, but this was not measured in the trials. Patient adherence is reported to be better with antihypertensive agents than with statins.<sup>64</sup> In addition, lifestyle modifications<sup>65 66</sup> also contribute to patients' clinical outcomes and may have played an important role in improving blood pressure control. More work is needed to disentangle the associations. In particular, because our analyses for blood pressure and LDL-C/cholesterol levels were based on a few studies only.

Our findings are consistent with previous systematic reviews<sup>28 29</sup> reporting professional and organisational as the two main types of interventions to improve healthcare

professionals' adherence to cardiovascular disease guidelines. Our study and a systematic review by Jeffery *et al*<sup>28</sup> showed only some significant improvements. A systematic review by Unverzagt *et al*,<sup>29</sup> in contrast, showed that a provider reminder system, audit and feedback, provider education or organisational change were effective interventions. However, results are difficult to compare as we measured different outcomes. We analysed the improvement of prescribing for each medication separately while both review articles<sup>28 29</sup> took all medication together. Moreover, we focused on patients with IHDs, whereas previous reviews<sup>28 29</sup> included different cardiovascular diseases. Although programmes promoting guidelines such as the Guidelines Applied in Practice and Get With The Guidelines programmes also involving organisational and professional interventions demonstrated that it was possible to improve quality of care,<sup>67</sup> the design of RCT is needed to confirm the improvement.

Several issues need to be addressed in our study. First, there were seven studies rated as having a high risk of other bias. Of these studies, six cluster RCTs<sup>50 52 53 56-58</sup> had a high risk of recruitment bias. In those studies, patients were recruited after the clusters had been randomised and therefore, the knowledge of whether a cluster belonged to the intervention or control group could have affected patient recruitment. Farrin *et al*<sup>68</sup> showed this in a trial of low back pain randomised by primary care practice; a greater number of less severe participants were recruited to the 'active management' practices. However, we did not find significant differences in outcomes between RCTs<sup>45 49 51 59</sup> and cluster RCTs.<sup>43 47 50 52 53 55-58</sup> Second, there were some cluster RCTs<sup>47 50 53 56 58</sup> which did not report the ICCs. We used the mean ICCs for corresponding outcomes reported in the other included studies.<sup>39</sup> The sensitivity analyses without adjusting for clustering effects showed similar results. The heterogeneity became substantial for the outcomes of aspirin/antiplatelet agents, the composite of medications and target LDL-C/cholesterol. But overall, the sensitivity analyses confirmed the robustness of our findings. Third, we included studies of all types of interventions targeted at healthcare professionals in the meta-analyses. Subgroup analyses showed that there was no significant difference between subgroups of interventions (professional, organisational and professional plus organisational). But more detailed analyses, for example, on duration or intensity of the intervention, were impossible due to the limited number of studies. The length of patient follow-up varied across studies. This issue might increase the clinical heterogeneity of outcomes measured. Fourth, we included studies reporting patient-level outcomes, and excluded studies only reporting cluster-level outcomes (eg, hospital and practice performance scores).<sup>69 70</sup> Fifth, we performed multiple statistical tests which increased the risk of type I error. Adjustment for multiple testing is debatable.<sup>71</sup> In our study, three out of four primary outcomes were not significant, P value threshold adjustment would be too conservative. Finally, our review included only grey studies published in English and we did not search for grey literature. So we

may have missed relevant unpublished or locally published studies.

Our results have several implications for practice and research. Eleven out of 13 studies come from North America and Europe, which limits the generalisability of our results to the rest of the world. There maybe a need to develop new interventions, especially for low-income and middle-income countries which have a rising burden of ischaemic heart diseases. There are some types of interventions such as financial and regulatory that have not been tested in this group.<sup>26 27 72</sup> Selecting an intervention to enhance prescribing according to guidelines should be based on the local context. Interventions need to consider a range of barriers to change prescribing, including barriers related to patients, organisation of the healthcare system and resource constraints.<sup>31</sup> Finally, improving guideline adherence may include strategies for improving clinicians' awareness, agreement and adoption of guidelines. The cost-effectiveness of such interventions should also be evaluated.<sup>73–77</sup>

## CONCLUSIONS

In conclusion, a number of organisational and professional interventions improved prescribing of statins/lipid-lowering agents and target blood pressure in patients with IHDs, but there was little evidence of change in other outcomes.

### Author affiliations

<sup>1</sup>Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam

<sup>2</sup>Groningen Research Institute of Pharmacy, Unit of Pharmacotherapy, Epidemiology & Economics, University of Groningen, Groningen, The Netherlands

<sup>3</sup>Department of Clinical Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Ho Chi Minh, Vietnam

<sup>4</sup>Division of Management and Community Pharmacy, Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia

<sup>5</sup>Faculty of Public Health, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam

**Acknowledgements** The authors would like to thank Alice Fuller, BSc, and Michael Moher, MD (Nuffield Department of Primary Care Health Sciences, University of Oxford, UK) for providing additional data from their study. None of these individuals was compensated in association with their contributions to this article.

**Contributors** TN had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: TN, KT. Acquisition, analysis or interpretation of data: TN, HQN, NNW, KT. Drafting of the manuscript: TN, KT. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: TN. Obtained funding: TN. Administrative, technical or material support: THN, TTP, KT. Study supervision: THN, TTP, KT.

**Funding** This study was supported by the Vietnam International Education Development via the Project of Training Lecturers with PhD Degree for Universities and Colleges in the period from 2010 to 2020 (Project 911).

**Competing interests** None declared.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data available.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

## REFERENCES

- World Health Organization. *The top 10 causes of death*, 2017.
- World Health Organization. *International statistical classification of diseases and related health problems 10th revision (ICD-10)-WHO Version for 2016*, 2016.
- Steg PG, James SK, Atar D, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569–619.
- O'Gara PT, Kushner FG, Ascheim DD, *et al.* ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *Circulation* 2013;127:e362–425.
- Montalescot G, Sechtem U, Achenbach S, *et al.* ESC guidelines on the management of stable coronary artery disease. *Eur Heart J* 2013;34:2949–3003.
- Amsterdam EA, Wenger NK, Brindis RG, *et al.* AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *Circulation* 2014;130:e344–426.
- Fihn SD, Gardin JM, Abrams J, *et al.* ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *Circulation* 2012;126:e354–471.
- Roffi M, Patrono C, Collet J-P, *et al.* 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2016;37:267–315.
- Horning KK, Hoehns JD, Doucette WR. Adherence to clinical practice guidelines for 7 chronic conditions in long-term-care patients who received pharmacist disease management services versus traditional drug regimen review. *J Manag Care Pharm* 2007;13:28–36.
- Libungan B, Stensdotter L, Hjalmarson A, *et al.* Secondary prevention in coronary artery disease. Achieved goals and possibilities for improvements. *Int J Cardiol* 2012;161:18–24.
- Setoguchi S, Glynn RJ, Avorn J, *et al.* Improvements in long-term mortality after myocardial infarction and increased use of cardiovascular drugs after discharge: a 10-year trend analysis. *J Am Coll Cardiol* 2008;51:1247–54.
- Eagle KA, Montoye CK, Riba AL, *et al.* Guideline-based standardized care is associated with substantially lower mortality in medicare patients with acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan. *J Am Coll Cardiol* 2005;46:1242–8.
- Wijeyesundera HC, Machado M, Farahati F, *et al.* Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994–2005. *JAMA* 2010;303:1841–7.
- Bhatt DL, Steg PG, Ohman EM, *et al.* International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;295:180–9.
- Lee HY, Cooke CE, Robertson TA. Use of secondary prevention drug therapy in patients with acute coronary syndrome after hospital discharge. *J Manag Care Pharm* 2008;14:271–80.
- Newby LK, LaPointe NM, Chen AY, *et al.* Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation* 2006;113:203–12.
- Engel J, Damen NL, van der Wulp I, *et al.* Adherence to cardiac practice guidelines in the management of non-st-elevation acute coronary syndromes: a systematic literature review. *Curr Cardiol Rev* 2017;13:3–27.
- Forsetlund L, Børndal A, Rashidian A, *et al.* Continuing education meetings and workshops: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2009;(2):CD003030.
- Giguère A, Légaré F, Grimshaw J, *et al.* Printed educational materials: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012;10:CD004398.
- O'Brien MA, Rogers S, Jamtvedt G, *et al.* Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2007;17:CD000409.
- Reeves S, Perrier L, Goldman J, *et al.* Interprofessional education: effects on professional practice and healthcare outcomes (update). *Cochrane Database Syst Rev* 2013;(3):CD002213.
- Arditi C, Rège-Walther M, Wyatt JC, *et al.* Computer-generated reminders delivered on paper to healthcare professionals; effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2012;12:CD001175.

23. Ivers N, Jamtvedt G, Flottorp S, *et al*. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012;CD000259.
24. Damiani G, Pinnarelli L, Colosimo SC, *et al*. The effectiveness of computerized clinical guidelines in the process of care: a systematic review. *BMC Health Serv Res* 2010;10(6):2.
25. Nkansah N, Mostovetsky O, Yu C, *et al*. Effect of outpatient pharmacists' non-dispensing roles on patient outcomes and prescribing patterns. *Cochrane Database Syst Rev* 2010;(7):CD000336.
26. Rashidian A, Omidvari AH, Vali Y, *et al*. Pharmaceutical policies: effects of financial incentives for prescribers. *Cochrane Database Syst Rev* 2015;(8):CD006731.
27. Luiza VL, Chaves LA, Silva RM, *et al*. Pharmaceutical policies: effects of cap and co-payment on rational use of medicines. *Cochrane Database Syst Rev* 2015;(5):CD007017.
28. Jeffery RA, To MJ, Hayduk-Costa G, *et al*. Interventions to improve adherence to cardiovascular disease guidelines: a systematic review. *BMC Fam Pract* 2015;16:147.
29. Unverzagt S, Oemler M, Braun K, *et al*. Strategies for guideline implementation in primary care focusing on patients with cardiovascular disease: a systematic review. *Fam Pract* 2014;31:247–66.
30. Murphy E, Vellinga A, Byrne M, *et al*. Primary care organisational interventions for secondary prevention of ischaemic heart disease: a systematic review and meta-analysis. *Br J Gen Pract* 2015;65:e460–8.
31. Flottorp SA, Oxman AD, Krause J, *et al*. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. *Implement Sci* 2013;8:35.
32. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
33. In: Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions version 5.1.0*. The Cochrane Collaboration, 2016. Updated Mar 2011.
34. Nguyen T, Widyakusuma NN, Nguyen HQ, *et al*. Interventions to enhance prescribing guideline-recommended medications for patients with ischemic heart diseases: a systematic review and meta-analysis. *PROSPERO* 2016:CRD42016039188.
35. *Effective Practice and Organisation of Care (EPOC). Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors*. Oslo: Norwegian Knowledge Centre for the Health Services, 2015:2016.
36. *Effective Practice and Organisation of Care (EPOC). Type of intervention. EPOC resources for review authors*. oslo: Norwegian knowledge centre for the health services, 2016.
37. The Cochrane Collaboration. Review manager (revman) [computer program]. Version 5.3. 2014.
38. Donner A, Piaggio G, Villar J. Statistical methods for the meta-analysis of cluster randomization trials. *Stat Methods Med Res* 2001;10:325–38.
39. Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Stat Med* 2002;21:2971–80.
40. Schünemann H, Brozek J, Guyatt G, Oxman A, eds. *Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach*. 2016, 2013.
41. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
42. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
43. Berwanger O, Guimarães HP, Laranjeira LN, *et al*. Effect of a multifaceted intervention on use of evidence-based therapies in patients with acute coronary syndromes in Brazil: the BRIDGE-ACS randomized trial. *JAMA* 2012;307:2041–9.
44. Berwanger O, Guimarães HP, Laranjeira LN, *et al*. A multifaceted intervention to narrow the evidence-based gap in the treatment of acute coronary syndromes: rationale and design of the Brazilian Intervention to Increase Evidence Usage in Acute Coronary Syndromes (BRIDGE-ACS) cluster-randomized trial. *Am Heart J* 2012;163:323–9.
45. Community Pharmacy Medicines Management Project Evaluation Team. The MEDMAN study: a randomized controlled trial of community pharmacy-led medicines management for patients with coronary heart disease. *Fam Pract* 2007;24:189–200.
46. Flather MD, Booth J, Babalis D, *et al*. Improving the management of non-ST elevation acute coronary syndromes: systematic evaluation of a quality improvement programme European Quality Improvement Programme for Acute Coronary Syndrome: the EQUIP-ACS project protocol and design. *Trials* 2010;11:5.
47. Flather MD, Babalis D, Booth J, *et al*. Cluster-randomized trial to evaluate the effects of a quality improvement program on management of non-ST-elevation acute coronary syndromes: the European Quality Improvement Programme for Acute Coronary Syndromes (EQUIP-ACS). *Am Heart J* 2011;162:700–7.
48. Funkhouser E, Levine DA, Gerald JK, *et al*. Recruitment activities for a nationwide, population-based, group-randomized trial: the VA MI-Plus study. *Implement Sci* 2011;6:105.
49. Garcia BH, Giverhaug T, Høglø JU, *et al*. A pharmacist-led follow-up program for patients with established coronary heart disease in North Norway - a randomized controlled trial. *Pharm Pract* 2015;13:575.
50. Guadagnoli E, Normand SL, DiSalvo TG, *et al*. Effects of treatment recommendations and specialist intervention on care provided by primary care physicians to patients with myocardial infarction or heart failure. *Am J Med* 2004;117:371–9.
51. Hung CS, Lin JW, Hwang JJ, *et al*. Using paper chart based clinical reminders to improve guideline adherence to lipid management. *J Eval Clin Pract* 2008;14:861–6.
52. Khunti K, Stone M, Paul S, *et al*. Disease management programme for secondary prevention of coronary heart disease and heart failure in primary care: a cluster randomised controlled trial. *Heart* 2007;93:1398–405.
53. Levine DA, Funkhouser EM, Houston TK, *et al*. Improving care after myocardial infarction using a 2-year internet-delivered intervention: the Department of Veterans Affairs myocardial infarction-plus cluster-randomized trial. *Arch Intern Med* 2011;171:1910–7.
54. McAlister FA, Fradette M, Graham M, *et al*. A randomized trial to assess the impact of opinion leader endorsed evidence summaries on the use of secondary prevention strategies in patients with coronary artery disease: the ESP-CAD trial protocol [NCT00175240]. *Implement Sci* 2006;1:11.
55. McAlister FA, Fradette M, Majumdar SR, *et al*. The enhancing secondary prevention in coronary artery disease trial. *CMAJ* 2009;181:897–904.
56. Moher M, Yudkin P, Wright L, *et al*. Cluster randomised controlled trial to compare three methods of promoting secondary prevention of coronary heart disease in primary care. *BMJ* 2001;322:1338.
57. Ornstein S, Jenkins RG, Nietert PJ, *et al*. A multimethod quality improvement intervention to improve preventive cardiovascular care: a cluster randomized trial. *Ann Intern Med* 2004;141:523–32.
58. Søndergaard J, Hansen DG, Aarslev P, *et al*. A multifaceted intervention according to the audit project odense method improved secondary prevention of ischemic heart disease: a randomised controlled trial. *Fam Pract* 2006;23:198–202.
59. Yorio J, Viswanathan S, See R, *et al*. The effect of a disease management algorithm and dedicated postacute coronary syndrome clinic on achievement of guideline compliance: results from the parkland acute coronary event treatment study. *J Investig Med* 2008;56:15–25.
60. Chen YF, Hemming K, Stevens AJ, *et al*. Secular trends and evaluation of complex interventions: the rising tide phenomenon. *BMJ Qual Saf* 2016;25:303–10.
61. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol* 2014;67:267–77.
62. Beaulieu MD, Brophy J, Jacques A, *et al*. Physicians' attitudes to the pharmacological treatment of patients with stable angina pectoris. *QJM* 2005;98:41–51.
63. Ribeiro RA, Ziegelmann PK, Duncan BB, *et al*. Impact of statin dose on major cardiovascular events: a mixed treatment comparison meta-analysis involving more than 175,000 patients. *Int J Cardiol* 2013;166:431–9.
64. Chowdhury R, Khan H, Heydon E, *et al*. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940–8.
65. de Waure C, Lauret GJ, Ricciardi W, *et al*. Lifestyle interventions in patients with coronary heart disease: a systematic review. *Am J Prev Med* 2013;45:207–16.
66. Janssen V, De Gucht V, Dusseldorp E, *et al*. Lifestyle modification programmes for patients with coronary heart disease: a systematic review and meta-analysis of randomized controlled trials. *Eur J Prev Cardiol* 2013;20:620–40.
67. Van de Werf F, Ardissino D, Bueno H, *et al*. Acute coronary syndromes: considerations for improved acceptance and implementation of management guidelines. *Expert Rev Cardiovasc Ther* 2012;10:489–503.
68. Farrin A, Russell I, Torgerson D, *et al*. Differential recruitment in a cluster randomized trial in primary care: the experience of the UK

- back pain, exercise, active management and manipulation (UK BEAM) feasibility study. *Clin Trials* 2005;2:119–24.
69. Fihn SD, Bucher JB, McDonell M, *et al*. Collaborative care intervention for stable ischemic heart disease. *Arch Intern Med* 2011;171:1471–9.
70. Lytle BL, Li S, Lofthus DM, *et al*. Targeted versus standard feedback: results from a randomized quality improvement trial. *Am Heart J* 2015;169:132–41.
71. Jakobsen JC, Wetterslev J, Lange T, *et al*. Viewpoint: taking into account risks of random errors when analysing multiple outcomes in systematic reviews. *Cochrane Database Syst Rev* 2016;3:ED000111.
72. Flodgren G, Eccles MP, Shepperd S, *et al*. An overview of reviews evaluating the effectiveness of financial incentives in changing healthcare professional behaviours and patient outcomes. *Cochrane Database Syst Rev* 2011;(7):CD009255.
73. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev* 2005;4:CD003539.
74. Arts DL, Voncken AG, Medlock S, *et al*. Reasons for intentional guideline non-adherence: A systematic review. *Int J Med Inform* 2016;89:55–62.
75. Cabana MD, Rand CS, Powe NR, *et al*. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458–65.
76. Mickan S, Burls A, Glasziou P. Patterns of 'leakage' in the utilisation of clinical guidelines: a systematic review. *Postgrad Med J* 2011;87:670–9.
77. Sadeghi-Bazargani H, Tabrizi JS, Azami-Aghdash S. Barriers to evidence-based medicine: a systematic review. *J Eval Clin Pract* 2014;20:793–802.