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A systematic review and meta-analysis of pharmacist-led fee-for-services medication review

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AIM
The aim was to examine the impact of fee-for-service pharmacist-led medication review on patient outcomes and quantify this according to the type of review undertaken, e.g. adherence support and clinical medication review.

METHODS
Relevant published studies were identified from Medline, Embase and International Pharmaceutical Abstract databases (from inception to February 2011). Study inclusion criteria were fee-for-service medication review, presence of a control group and pre-specified patient outcomes. Outcomes were grouped into primary (changes in biomarkers, hospitalization, and mortality) and secondary outcomes (medication adherence, economic implications and quality of life). Meta-analyses for primary outcomes were conducted using random effects models and secondary outcomes were summarized using descriptive statistics.

RESULTS
Of the 135 relevant articles located, 21 studies met the inclusion criteria for primary outcomes and 32 for secondary outcomes. Significant results favouring pharmacists' intervention were found for blood pressure (OR 3.50, 95% CI 1.58, 7.75, $P = 0.002$) and low density lipoprotein (OR 2.35, 95% CI 1.17, 4.72, $P = 0.02$). Outcomes on hospitalization (OR 0.69, 95% CI 0.39, 1.21, $P = 0.19$) and mortality (OR 1.50, 95% CI 0.65 to 3.46, $P = 0.34$) indicated no differences between the groups. On subgroup analysis, clinical medication review (OR 0.46, 95% CI 0.26, 0.83, $P = 0.01$) but not adherence support review (OR 0.88, 95% CI 0.59, 1.32, $P = 0.54$) reduced hospitalization.

CONCLUSIONS
The majority of the studies (57.9%) showed improvement in medication adherence. Fee-for-service pharmacist-led medication reviews showed positive benefits on patient outcomes. Interventions that include a clinical review had a significant impact on patient outcomes by attainment of target clinical biomarkers and reduced hospitalization.

Introduction

Medication review can be defined as a structured, critical examination of a patient's medications with the objectives of reaching an agreement with the patient about their treatment and optimizing the impact of medications on patient's health outcomes [1]. Pharmacist-led medication review services are available in several countries such as the United Kingdom (UK) (Medicines Use Review, MUR), United States of America (USA) (Medication Therapy Management, MTM), Australia (Home Medication Review, HMR), Canada (MedsCheck) and New Zealand (Medicines Use Review, MUR) [1–5].

Medication review can be classified into four types: (1) prescription review, (2) adherence support review, (3) clinical review and (4) clinical review with prescribing [1, 5]. (1) A prescription review aims to address the technical issues of a patient's prescription such as anomalies or changed items [1]. (2) An adherence support review, with the patient present, addresses a patient's medication-taking behaviour focusing on improving a patient's knowledge of medicines and adherence to

them [1]. (3) A clinical medication review, with access to clinical notes and the patient present, is more comprehensive and addresses the patients' use of medication in the context of their clinical condition [6] (4) In some countries an extension of type 3 exists and includes the authority for prescribing [5]. These services, the last two particularly, must be conducted in close collaboration with physicians and other health professionals [2].

As previously mentioned several countries pay pharmacists for providing medication reviews for patients [1–4, 7]. These can be termed 'fee-for-service' medication reviews because pharmacists are remunerated by the government or a health provider for each item of service or under bulk funding or capitation models. To our knowledge no review has assessed the clinical benefits of fee-for-service medication reviews where pharmacists carry out these reviews in their usual practice settings (with time, staffing and resource constraints) and not in a highly controlled research environment [8]. Furthermore no research has been published to quantify the effect of medication review by its type. A pooled meta-analysis of all types will hide the individual influences of these services.

The current study therefore aimed to examine the impact of fee-for-service pharmacist-led medication review on patient outcomes and quantify these according to the type of review undertaken. The specific objectives were to evaluate and quantify (i) the primary outcomes of such services (such as hospitalization, mortality rate, clinical biomarkers or marker of disease progress) and (ii) any secondary outcomes (such as medication adherence, economic implications and quality of life).

Methods

Locating studies

Studies were located through a comprehensive literature search of electronic bibliographic databases of Medline (1946–February 2011), Embase (1947–February 2011) and International Pharmaceutical Abstracts (IPA) (1970–February 2011). The current study used a learning based search algorithm [9] to provide appropriate coverage of the databases.

Identifying relevant subject headings and locating articles

Details of the learning-based search algorithm have been described elsewhere [9]. An article by Planas *et al*. (2009) was used as the index article in the learning algorithm to find the relevant subject headings (SH). The relevant SH from the index articles: community pharmacy services.exp*, patient compliance.exp, quality of health care.exp, treatment outcome.exp, Medication Therapy Management.exp (for Medline), pharmacy.exp*, health care quality.exp, patient compliance.exp, treatment outcome.exp, Medication Therapy Management.exp (for Embase) and pharmacy community.sh*, pharmacy.sh, interventions.sh, compliance.sh, quality assurance.sh (for IPA), were combined to retrieve more articles. Regardless of the relevance of the article to the review topic, relevant SH from the article were used in combination with the Boolean operator 'AND', to increase specificity. Combinations of four (Medline and Embase) and five (IPA) SH were considered to produce an acceptable number of hits to review. All permutations were considered. A fixed subject heading, marked with * was always included in each combination. The next iteration of the search continued until no new relevant SH were found. At the end of the search, articles that were located from each combination were pooled using 'OR' to eliminate duplicates. SH used to retrieve the articles are listed in Appendix S1.

Study selection

After the learning-based search algorithm had converged, articles were imported into EndNote and screened for prespecified inclusion and exclusion criteria (Table 1). Since the present study focused on 'fee-for-service' medication reviews that occur in usual care settings (not in a highly controlled research environment), we considered both randomized controlled trials (RCTs) and non-randomized controlled trials (non-RCTs) should be included. Although RCTs are the best study design for such services, it is not convenient in all situations to conduct RCTs for fee-for-service medication reviews (for example if the service has been provided to patients before the study begins). Hence the present study also included non-RCT studies.

Initial titles/abstracts screening was conducted by EH. The exclusion process using titles/abstracts by EH only occurred if the reason for exclusion was clear. If there was uncertainty the article was not excluded and each member of the research team (EH, JT, RB, SD) then reviewed the articles. All excluded 'full text' articles were reviewed by EH, JT, RB and SD independently to ensure the validity of the process and any disagreements on whether a study should be included/excluded were resolved through consensus. Since prescription review (type 1) is usually considered as part of pharmacists' routine in medication dispensing, this service is not considered in this review.

Data extraction

Data extracted from a full-text report using a data extraction form included study characteristics, participant characteristics, type of intervention/services and study outcomes. Medication reviews were categorized by type based on objective descriptions (see Table 2**).**

Patient outcomes reported in each study were categorized into primary and secondary outcomes. Our categories on types of outcomes were based on how the outcomes reflect in patients' wellbeing. We defined primary outcomes as those that were considered as either

Table 1

Inclusion and exclusion criteria for systematic review of fee-for-service medication review

Inclusion criteria	
Study design	• Randomized controlled trial, quasi-experiment with control group, before and after study design or prospective/retrospective cohort with control group
Participant	• Adult participants defined by the individual study
Setting	• Intervention was conducted in the following setting: pharmacy, patients' home, community health centre, GP clinics
Intervention	• A medication review service: Medication review involved pharmacists providing pharmaceutical care and/or equivalent service to a patient. The current study considered a service as a medication review if the intervention included (a) and at least two of the following activities: a) Review patient's medications for medication related issues b) Taking and documenting medication history c) Educating and counselling patients about medication and/or disease d) Providing a medication action plan e) Reaching an agreement with the patient about their medication treatment plan f) Monitoring drug treatment for effectiveness or adverse event g) Optimizing medication effectiveness and minimizing problems related to medication usage. • Pharmacists were reimbursed for the intervention. The intervention was considered as 'fee-for service' if: a) The country was known to provide funding for the particular service (e.g. Home Medication Review in Australia) b) The service was a demonstration/pilot service that received funding from interested parties (e.g. non-government agencies or university) c) The service received funding from independent parties such as patients, an employer or insurance company d) The service received funding through individual contracts with health agencies (e.g. District Health Board)
Comparison	• The intervention must be compared with a control group that received usual care
Outcomes	• Quantitative: (1) Primary outcomes such as mortality, hospitalization and clinical biomarkers or marker of disease progress (2) Secondary outcomes such as medication adherence, economic and quality of life For clinical biomarkers or marker of disease progress, data were included if the number of patients who achieved the target goal was defined or if mean and standard deviation (SD) or 95% confidence interval (95% CI) of the biomarker was reported. Only reported biomarkers that were assumed to be normally distributed were included in meta-analysis
Exclusion criteria	
Study design	• Review articles, commentaries, editorial letters and studies without a control group
Participants	• Intervention conducted only on paediatric patients or patients unable to give consent (e.g. patients with dementia)
Setting	• Intervention in nursing home or assisted living facilities, academic setting, hospital, out-patient setting and call centre
Interventions	• Intervention that only involved a prescription review (e.g. type 1 medication review) • Intervention that was not a medication review (e.g. smoking cessation clinic) • Pharmacist was only partly involved in delivering the medication review (combined interventions with other health professionals so that pharmacist's intervention cannot be distinctly quantified) • Intervention that was delivered only through phone calls or by pharmacy students • Intervention that was not reimbursed (e.g. a study funded through a University) or if: a) a fee was only provided for preparing and dispensing patient's medications
Outcomes	• Qualitative outcomes (e.g. perceptions that were not quantified) • Process outcomes (e.g. number of medication related problems identified or number of recommendations being accepted by doctors)

directly affecting a patient's wellbeing or were a marker of disease progress such as mortality, hospitalization, changes in clinically important biomarkers, e.g. glycosylated haemoglobin, blood pressure, low density lipoprotein (LDL), opportunistic infection, asthma severity/control score. Secondary outcomes were those considered to indirectly reflect patient outcomes: medication adherence scores, quality of life and economic outcomes.

Appraisal of studies

The quality of the studies was assessed for potential bias in accordance with the Cochrane Collaboration guidelines [10, 11]. A summary of the quality assessment criteria used is provided in Appendix S2.

Data analysis

Meta-analyses were only conducted for primary outcomes as the definition and measurement of the outcomes, such as blood pressure and hospitalization, were more standardized and less varied than outcomes in the secondary group. Secondary outcomes were evaluated and summarized using descriptive statistics.

For the meta-analysis, outcomes were categorized into the number of successes or failures. Success was defined respectively as the number of patients who achieved the clinical biomarker goal defined in the studies, were not hospitalized or who survived. For studies that only reported mean and SD or 95% CI, the number of patients achieving the target goal was calculated assuming the data conformed to a normal distribution. Data were not assumed to be normally distributed, and were excluded from meta-analysis, if the number of samples was small ($n < 30$), a large amount of data was near zero or at a natural limit.

Summary effect size was pooled if there were at least four studies reporting the outcomes. Data were entered into the RevMan software (Ver 5.1, Cochrane library). For all analyses a random effects model was used to estimate the

Table 2

Objective descriptions of type of medication review by pharmacists

Type*	Name of service	Possible intervention provided
2	Adherence review e.g. Medicines Use Review (MUR)	Addresses issues relating to a patients' medication taking behaviour, advice on medications use e.g. adverse effects, checking patients' technique and use of medication dosage forms e.g. inhalers, identify need for a change in dosage form.
3	Clinical medication review	Addresses issues relating to a patients' use of medication in the context of their clinical condition such as the appropriateness, effectiveness, cost-effectiveness and monitoring required to meet the patient's needs. The intervention must be face to face with the patient and it could be with or without full patients' clinical notes.
4	Clinical medication review and prescribing	As in type 3 but pharmacist had the ability to prescribe or adjust the medication dose (either in a supplementary or fully independent role)

*For all types of medication review, the pharmacist should consider drug interactions, side effects, adherence to medications, lifestyle, non-medication interventions and unmet need.

odds ratio (OR) in order to allow for study heterogeneity. Sensitivity analyses were performed to assess for studies that might be influential outliers on primary end points [12]. A one-study-removal method [13, 14] was used to examine the robustness of the results. A pre-specified subgroup analysis on the types of pharmacists' interventions (types 2–4, Table 2) was also conducted. For interest the present study also performed subgroup analysis on the types of study design (RCT *vs.* RCT and non-RCT). Publication bias was examined using funnel plots, the Begg-Mazumdar statistic ($P < 0.05$ for significance), classic fail-safe N and Duvel & Tweedie's Trim and Fill method.

Results

Details of the numbers of articles located and included/excluded for the systematic review are shown in Figure 1. Thirty-six articles were included in the systematic review and meta-analysis. Of these 21 studies reported primary outcomes of interest and 32 studies reported secondary outcomes.

Study characteristics

A summary of study characteristics for primary outcomes is presented in Table 3. Of the 36 studies, the majority of the medication reviews ($n = 30$) were disease-oriented interventions for patients with asthma ($n = 7$), diabetes ($n = 3$), hypertension ($n = 3$), hyperlipidaemia ($n = 3$), chronic diseases ($n = 5$) and other conditions ($n = 9$) such as stroke. Other services ($n = 6$) focused their interventions on the elderly ($n = 4$), patients newly discharged from hospital ($n = 1$) and patients with polypharmacy ($n = 1$).

Meta-analyses for primary outcomes were conducted for 21 studies (see Figure 1). Of the 21 studies, 13 (61.9%) were RCTs, seven (33.3%) were of prospective cohort and one (4.76%) was of retrospective cohort design. The majority ($n = 8$, 38.19%) of the studies were conducted in the USA, followed by in the UK ($n = 4$, 19%) and Canada ($n = 3$, 14.3%). Other studies were performed in the Netherlands ($n = 2$, 9.5%), Australia ($n = 2$, 9.5%), Belgium ($n = 1$, 4.8%) and Denmark ($n = 1$, 4.8%). Interventions were conducted mostly in a community pharmacy ($n = 9$, 42.9%), five studies (23.8%) in multiple settings (at the pharmacy and the patient's home), four (19%) at GP clinics/surgeries or at community health centres and three (14.3%) at the patient's home. The study quality assessment table is presented in Appendix S3.

Types of medication review were assigned to each study included in the meta-analysis. Five studies (23.8%) were classified as an adherence support review (type 2) and 13 studies (61.9%) were clinical medication reviews (type 3). Of the latter, half ($n = 7$, 33.3%) were conducted with some source of clinical information. Clinical medication review and prescribing (type 4) was described in two studies and one study was judged to be between types 2 and 3.

Primary outcomes: meta-analysis

Meta-analyses were conducted for the following outcomes: blood pressure ($n = 6$), low density lipoprotein (LDL) ($n = 4$), hospitalization ($n = 9$) and mortality ($n = 5$) (see Figure 2**)**. Pharmacist intervention was found to improve significantly the attainment of target biomarkers for blood pressure (OR 3.50, 95% CI 1.58, 7.75, $P = 0.002$) and LDL (OR 2.35, 95% CI 1.17, 4.72, $P = 0.02$) statistically. However there was no statistically significant difference found between pharmacists' interventions and usual care for hospitalization (OR 0.69, 95% CI 0.39, 1.21, $P = 0.19$) or mortality (OR 1.50, 95% CI 0.65, 3.46, $P = 0.34$).

Meta-analysis was also conducted on combined primary outcomes and only one outcome per study was included in the analysis. The primary outcome from the study was selected, or if there were multiple primary outcomes, then the outcome that had the largest number of participating patients was selected. In this analysis (Figure 3), patients who received fee-for–service medication reviews were found to achieve target clinical outcomes (e.g. biomarker target, less hospitalization, less mortality) more commonly than the patients in the usual care group (OR 1.46, 95% CI 1.15, 1.84, $P = 0.002$).

Subgroup analysis

Subgroup analysis according to type of interventions (e.g. adherence support review, clinical medication review), found a statistically significant reduction in the hospitali-

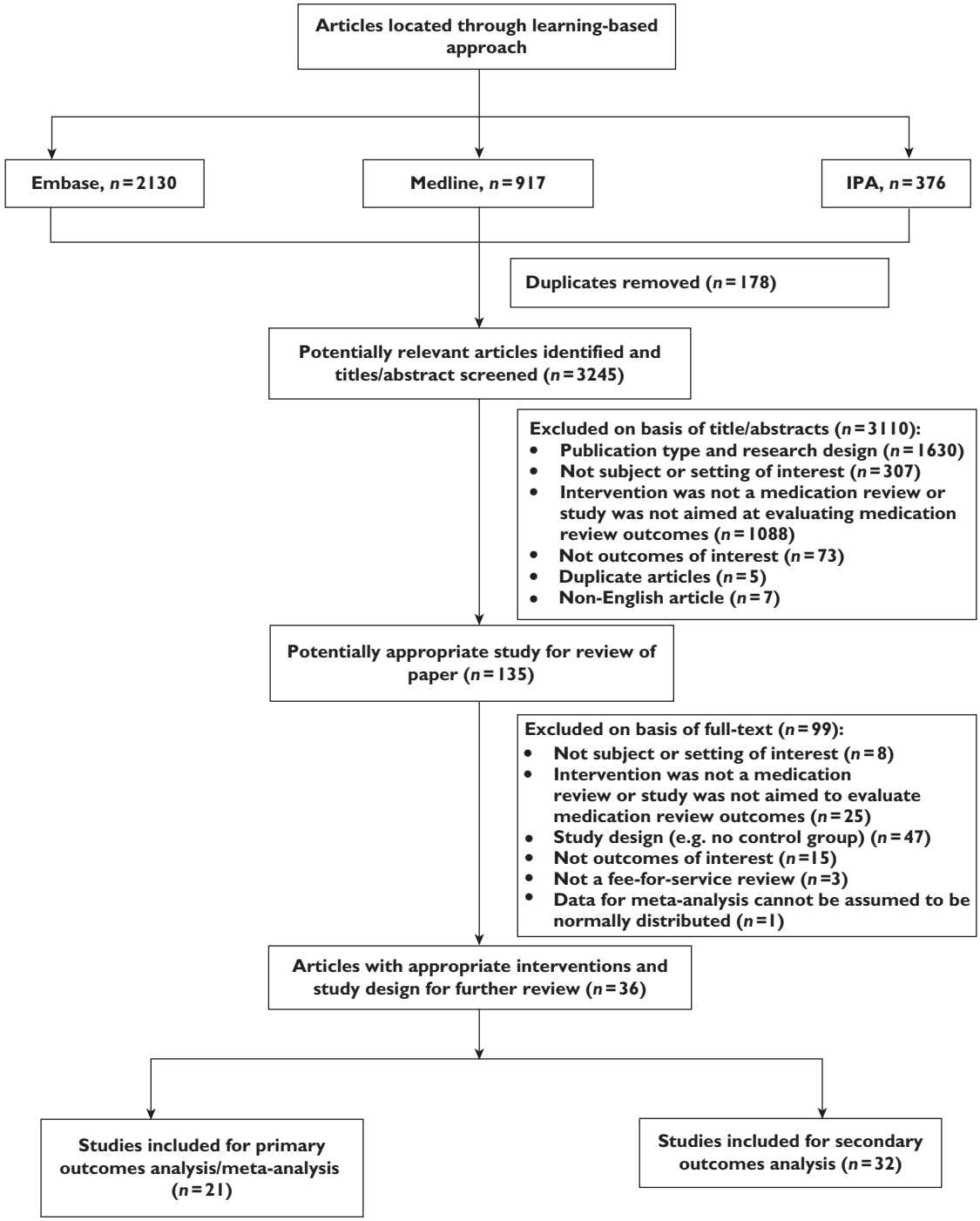


Figure 1
Systematic review inclusion and exclusion flowchart

zation rate in patients receiving a clinical medication review compared with patients having usual care (OR 0.46, 95% CI 0.26, 0.83, $P = 0.01$) (Figure 4). This was not seen for adherence support reviews when considered separately (OR 0.88, 95% CI 0.59, 1.32, $P = 0.54$). A similar pattern, favouring clinical medication review (OR 1.83, 95% CI 1.35, 2.49, $P = 0.0001$), was also seen in combined primary outcomes (see Appendix S4).

The only difference that was apparent when non-RCTs were removed from the analysis was for clinical medication review as the intervention, against the outcome of hospitalization (see Appendix 4). For this outcome there were

Table 3

Descriptions of studies and interventions

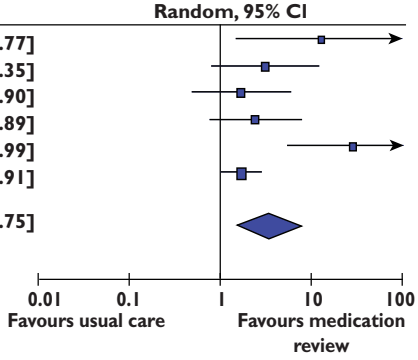
Author, year	Country	Study design	Number of patients (mean age ± SD) Intervention	Control	Patients' condition	Access to clinical notes*	Setting	Type of medication review	Primary outcome	Results#	Secondary outcome	Results#
Park *et al.* 1996 [20]	USA	RCT	27 (57.3)	25 (63)	Hypertension	No	Pharmacy	CMR	Blood pressure goal	NM	Compliance QoL	I > C I > C‡
Munroe *et al.* 1997 [21]	USA	Prospective cohort	188 (67.2 ± 12.6)	401 (63.3 ± 15.8)	Hypertension, diabetes, asthma, hypercholesterolaemia	Unclear	Pharmacy	CMR	–	–	Economics	I > C‡
Begley *et al.* 1997 [22]	UK	RCT	61 (84)	66 (82)	Discharge from hospital, elderly	No	Patient's home	AR	–	–	Compliance	I > C
Carter *et al.* 1997 [23]	USA	RCT	25 (67.3)	26 (68.5)	Hypertension	Yes	Pharmacy, patient's home	CMR	Blood pressure goal	I = C	Economics QoL	C > I NM
Anonymous 2000 [24]	USA	Prospective cohort	NM	NM	Asthma, hypertension, diabetes, ischaemic heart disease	Unclear	Pharmacy	CMR	–	–	Economics	NM
Cordina *et al.* 2001 [25]	UK	RCT (Cluster)	64 (41.3 ± 18.4)	55 (45.9 ± 18.1)	Asthma	Yes	Pharmacy	CMR	Self reported symptoms¤ Hospitalization	I > C I > C	ComplianceQoL	I = C I > C‡
Herborg *et al.* 2001 [26]	Denmark	Prospective cohort	209 (38.8 ± 12.3)	204 (42.4 ± 11.6)	Asthma	Unclear	Pharmacy	CMR	Hospitalization	I = C	QoL	I > C
Herborg *et al.* 2001 [27]	Denmark	Prospective cohort	167 (38.8 ± 12.3)	137 (42.4 ± 11.6)	Asthma	Unclear	Pharmacy	CMR	–	–	Compliance	I > C
Schulz *et al.* 2001 [28]	Germany	Prospective cohort	101 (46.3 ± 11.4)	63 (45.9 ± 12.5)	Asthma	Unclear	Pharmacy	AR	Asthma severity§	I = C	QoL	I > C‡
Finley *et al.* 2002 [29]	USA	Prospective cohort	61 (59.9 ± 15.9)	129 (61.1 ± 16.2)	Depression	No	GP clinic (Health centre), phone call	CMR with prescribing	–	–	Compliance	I > C
Fischer *et al.* 2002 [30]	USA	Prospective cohort	231 (57)	444 (58)	Heart and lung disease	Unclear	Pharmacy (community and health centre)	Unclear (between AR and CMR)	Mortality	I > C	Economics	I = C
Taylor *et al.* 2003 [31]	USA	RCT	25 (64.4 ± 13.7)	32 (66.7 ± 12.3)	Hypertension, diabetes, dyslipidemia, on warfarin	Yes	GP clinic	CMR	BP goal¤ LDL goal Hospitalization	I > C I > C I > C	Compliance QoL	I = C I = C
Sturgess *et al.* 2003 [32]	UK	RCT (Cluster)	75 (73.1 ± 5.0)	35 (74.2 ± 6.3)	Elderly	No	Pharmacy, patient's home	CMR	Hospitalization	I = C	Compliance QoL	I > C C > I‡
Sellors *et al.* 2003 [33]	Canada	RCT (Cluster)	379 (74 ± 6.1)	409 (74 ± 6.0)	Elderly	Yes	GP clinic	CMR	Hospitalization	NM	Economics QoL	I = C I = C
Chabot *et al.* 2003 [34]	Canada	Prospective cohort	35 (NM)	56 (NM)	Hypertension	No	Pharmacy	CMR	BP goal (high income)	I > C‡	Compliance (high income)	I > C‡
Bouvy *et al.* 2003 [35]	Netherland	RCT	48 (69.1 ± 10.2)	43 (70 ± 11.2)	Heart failure on loop diuretics	No	Pharmacy	AR	Hospitalization(((heart failure)¤ Mortality	I = C I = C	Compliance QoL (generic)	I > C C > I‡
Chrischilles *et al.* 2004 [36]	USA	Prospective cohort	524 (54.1 ± 0.8)	1687 (48.4 ± 0.5)	Polypharmacy	Unclear	Pharmacy	CMR	–	–	Economics	I = C
Krass *et al.* 2005 [37]	Australia	Prospective cohort	106 (64 ± 9)	82 (65 ± 10)	Type II diabetes	Unclear	Pharmacy	CMR	–	–	Compliance	I > C‡
Paulos *et al.* 2005 [38]	Chile	RCT	23 (64 ± 10)	19 (66 ± 11)	Dyslipidaemia	Unclear	Pharmacy	CMR	Total cholesterol†	NM	QoL	NM

Author, year	Country	Study design	Number of patients (mean age ± SD) Intervention	Control	Patients' condition	Access to clinical notes*	Setting	Type of medication review	Primary outcome	Results#	Secondary outcome	Results#
Shane-McWhorter *et al.* 2005 [39]	USA	Prospective cohort	151 (69.1 ± 13.8)	176 (54 ± 12.8)	Diabetes	Yes	GP clinic (Health centre)	CMR	Systolic blood pressure goal¤ LDL goal	I = C NM	–	–
Vrijens *et al.* 2006 [40]	Belgium	RCT	194 (61.9 ± 19)	198 (60.4 ± 10.2)	On atorvastatin	Yes	Pharmacy	AR	–	–	Compliance	I > C
Holland *et al.* 2007 [16]	UK	RCT	136 (77.6 ± 9.0)	144 (76.4 ± 9.5)	Heart failure	Yes	Patient's home	AR	HospitalizationMortality	I = C I = C	Compliance QoL	I = C I = C
Christensen *et al.* 2007 [41]	USA	Prospective before and after	67 (67.7 ± 11.4)	870 (66 ± 12.1)	Polypharmacy	Unclear	Pharmacy (community and health centre)	CMR	–	–	Economics	NM
Scott *et al.* 2007 [42]	UK	RCT	883 (68.7 ± 9.2)	472 (68.8 ± 9.1)	Coronary heart disease	Yes	Pharmacy	CMR	–	–	Economics	I > C‡
Armour *et al.* 2007 [43]	Australia	RCT (Cluster)	165 (47.5 ± 17.1)	186 (50.4 ± 16.1)	Asthma	Unclear	Pharmacy and patient's home	CMR	Asthma severity	I > C	Compliance QoL	I > C I > C
Lenaghan *et al.* 2007 [44]	UK	RCT	68 (84.5)	66 (84.1)	Elderly	Yes	Patient's home	AR	Hospitalization Mortality	¤ I = C I = C	QoL	I = C
Team 2007 [45]	UK	RCT	883 (68.7 ± 9.2)	472 (68.8 ± 9.1)	Coronary heart disease	Yes	Pharmacy	CMR	–	–	Compliance QoL	I = C I = C
Saini *et al.* 2008 [46]	Australia	Prospective cohort	46 (50.8 ± 15.3)	37 (50.4 ± 18.4)	Asthma	Unclear	Pharmacy and patient's home	CMR	Asthma severity†	I > C	Compliance QoL	I > C I = C
Mehuys *et al.* 2008 [47]	Belgium	RCT	80 (36.3)	70 (35.2)	Asthma	Unclear	Pharmacy	AR	Asthma control	I = C	Compliance QoL	I > C‡ I = C
Issets *et al.* 2008 [15]	USA	Prospective cohort	285 (NM)	126 (NM)	Had health claim on chronic disease	Unclear	GP clinic	CMR	Blood pressure goal¤ LDL goal	I > C I > C	–	–
Planas *et al.* 2009 [48]	USA	RCT	25 (64.2 ± 10.5)	15 (65.2 ± 14.1)	Diabetes with hypertension	Unclear	Pharmacy	CMR	Blood pressure goal	I > C	Compliance	I = C
Hugtenberg *et al.* 2009 [49]	Netherland	Prospective cohort	336 (69.7 ± 15.0)	379 (72.7 ± 11.2)	Discharge from hospital	No	Pharmacy, patient's home, phone call	AR	Mortality	I = C	–	–
Hirsch *et al.* 2009 [50]	USA	Prospective cohort	1353 (46)	5665 (46.7)	HIV/AIDS	No	Pharmacy	CMR	Opportunistic infection	I = C	Compliance Economics	I > C C > I
Roughead *et al.* 2009 [51]	Australia	Retrospective cohort	273 (81.6 ± 4.8)	5444 (81.6 ± 4.8)	Heart failure, elderly	Yes	Patient's home	CMR	Hospitalization	I > C	–	–
Hohmann *et al.* 2009 [52]	Germany	Prospective cohort	73 (68.2 ± 9.7)	157 (68.1 ± 10.8)	Transient ischaemic attack, ischaemic stroke	No	Pharmacy	Unclear (between AR and CMR)	–	–	QoL	I > C‡
Villeneuve *et al.* 2010 [53]	Canada	RCT (Cluster)	101 (59.3 ± 9.6)	110 (62.2 ± 12.0)	On statin with inadequate control	Yes	Pharmacy	CMR with prescribing	LDL target	I = C	Compliance	I = C

*Include summary/ discharge notes from doctors, #Results based on significant finding reported in individual study, QoL = Quality of Life. †=Not included in meta-analysis, =include in combined primary outcome meta-analysis. I > C = intervention is significantly better than control, I = C = no significant difference between intervention and control, NM = significant value for comparison between groups was not mentioned clearly/conducted or information was not available, C > I = control is significantly better than intervention. ‡Significant in certain domains/outcomes. AR, Adherence review; CMR Clinical medication review.

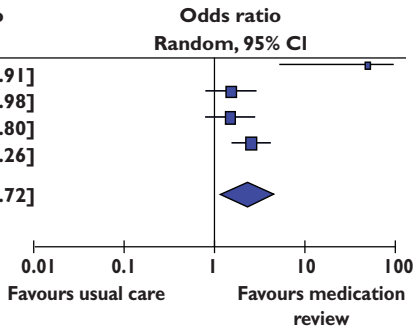
Blood pressure	Medication review		Usual care			Odds ratio	Odds ratio
Study	Success*	Total	Success*	Total	Weight	95% CI	Random, 95% CI
Planas *et al.* 2009 [48]	12	25	1	15	9.2%	12.92 [1.47, 113.77]	
Chabot *et al.* 2003 [34]	9	13	13	31	15.8%	3.12 [0.79, 12.35]	
Carter *et al.* 1997 [23]	17	23	15	24	17.3%	1.70 [0.49, 5.90]	
Park *et al.* 1996 [20]	12	23	8	26	18.2%	2.45 [0.76, 7.89]	
Taylor *et al.* 2003 [31]	22	24	8	29	13.0%	28.88 [5.49, 151.99]	
Issets *et al.* 2008 [15]	91	128	74	126	26.5%	1.73 [1.03, 2.91]	
Total (95% CI)		236		251	100.0%	3.50 [1.58, 7.75]	
Total events	163		119				

Heterogeneity: $Tau^2=0.55$; $Chi^2=12.88$, df=5 ($P=0.02$); $I^2=61\%$
Test for overall effect Z=3.09 ($P=0.002$)
*Success: achieving target blood pressure



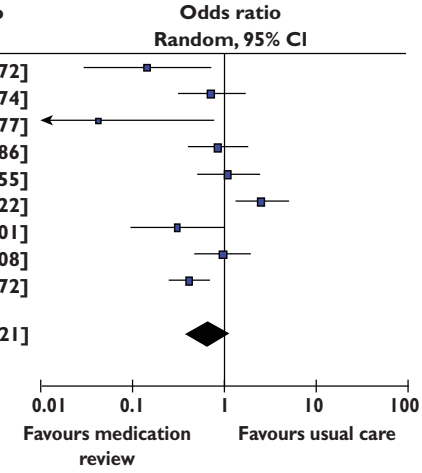
LDL cholesterol	Medication review		Usual care			Odds ratio	Odds ratio
Study	Success*	Total	Success*	Total	Weight	95% CI	Random, 95% CI
Taylor *et al.* 2003 [31]	14	19	1	19	7.7%	50.40 [5.27, 481.91]	
Shane-McWhorter *et al.* 2005 [39]	42	79	28	66	29.4%	1.54 [0.80, 2.98]	
Villeneuve *et al.* 2010 [53]	87	108	86	117	30.1%	1.49 [0.80, 2.80]	
Issets *et al.* 2008 [15]	67	128	38	126	32.8%	2.45 [1.52, 4.26]	
Total (95% CI)		334		328	100.0%	2.35 [1.17, 4.72]	
Total events	210		153				

Heterogeneity: $Tau^2=0.32$; $Chi^2=10.10$, df=3 ($P=0.02$); $I^2=70\%$
Test for overall effect Z=2.41 ($P=0.02$)
*Success: achieving target LDL



Hospitalisation	Medication review		Usual care			Odds ratio	Odds ratio
Study	Failure*	Total	Failure*	Total	Weight	95% CI	Random, 95% CI
Taylor *et al.* 2003 [31]	2	33	11	38	7.2%	0.15 [0.03, 0.72]	
Sturgess *et al.* 2003 [32]	23	75	13	35	12.3%	0.75 [0.32, 1.74]	
Cordina *et al.* 2001 [25]	0	64	8	55	3.1%	0.04 [0.00, 0.77]	
Lenaghan *et al.* 2007 [44]	20	68	21	68	13.2%	0.89 [0.43, 1.86]	
Bouvy *et al.* 2003 [35]	16	74	15	78	12.7%	1.16 [0.53, 2.55]	
Holland *et al.* 2007 [16]	134	148	112	143	13.6%	2.65 [1.34, 5.22]	
Herborg *et al.* 2001 [26]	4	210	11	190	9.8%	0.32 [0.10, 1.01]	
Sellors *et al.* 2003 [53]	15	379	16	409	13.3%	1.01 [0.49, 2.08]	
Roughead *et al.* 2009 [51]	15	273	653	5444	14.8%	0.43 [0.25, 0.72]	
Total (95% CI)		1324		6456	100.0%	0.69 [0.39, 1.21]	
Total events	229		860				

Heterogeneity: $Tau^2=0.48$; $Chi^2=29.51$, df=8 ($P=0.0003$); $I^2=73\%$
Test for overall effect Z=1.30 ($P=0.19$)
*Failure: hospitalization



Mortality	Medication review		Usual care			Odds ratio	Odds ratio
Study	Failure*	Total	Failure*	Total	Weight	95% CI	Random, 95% CI
Lenaghan *et al.* 2007 [44]	7	61	6	60	17.8%	1.17 [0.37, 3.70]	
Bouvy *et al.* 2003 [35]	31	71	4	74	18.3%	13.56 [4.46, 41.21]	
Holland *et al.* 2007 [16]	30	148	24	143	23.8%	1.26 [0.70, 2.28]	
Hugtenberg *et al.* 2009 [49]	74	262	83	296	25.7%	1.01 [0.70, 1.48]	
Fischer *et al.* 2002 [30]	2	229	11	433	14.3%	0.34 [0.07, 1.54]	
Total (95% CI)		771		1006	100.0%	1.50 [0.65, 3.46]	
Total events	144		128				

Heterogeneity: $Tau^2=0.67$; $Chi^2=21.81$, df=4 ($P=0.0002$); $I^2=82\%$
Test for overall effect Z=0.96 ($P=0.34$)
*Failure: mortality

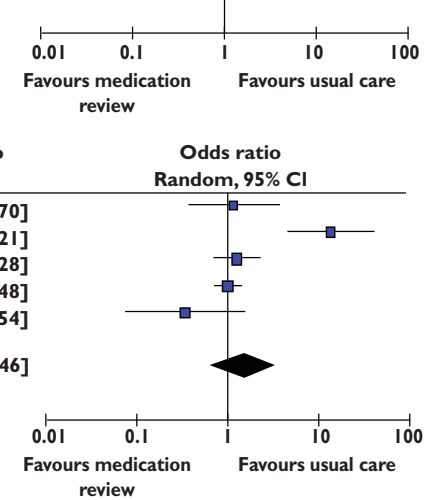


Figure 2

Forest plot for blood pressure, LDL, hospitalization and mortality outcomes. OR is >1 when medication review increased the number of patients achieving the target BP. OR is >1 when medication review increased the number of patients achieving the target LDL. OR is <1 when medication review reduced hospitalization. OR is <1 when medication review reduced mortality

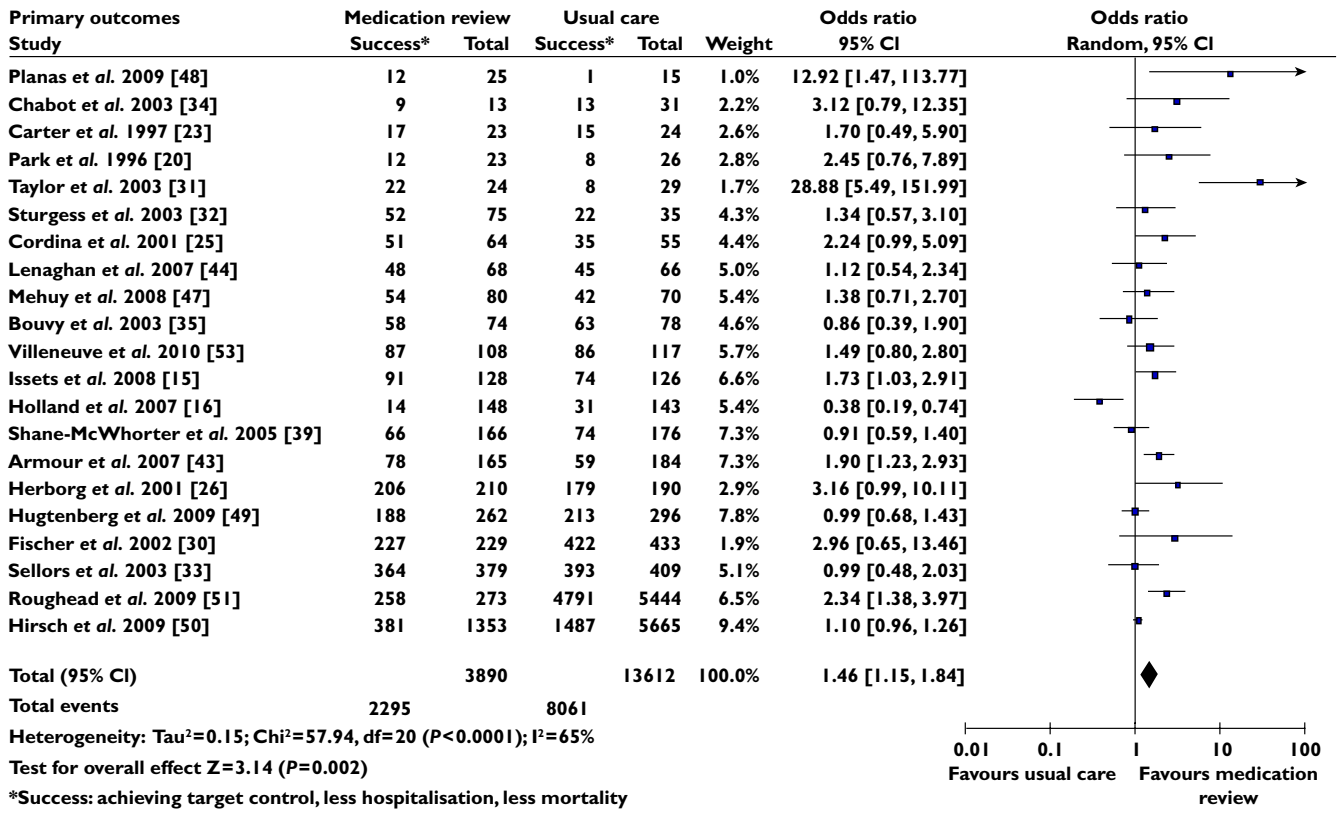


Figure 3

Forest plot of combined primary outcomes. OR is >1 when medication review decreased hospitalization or increased attainment of target control

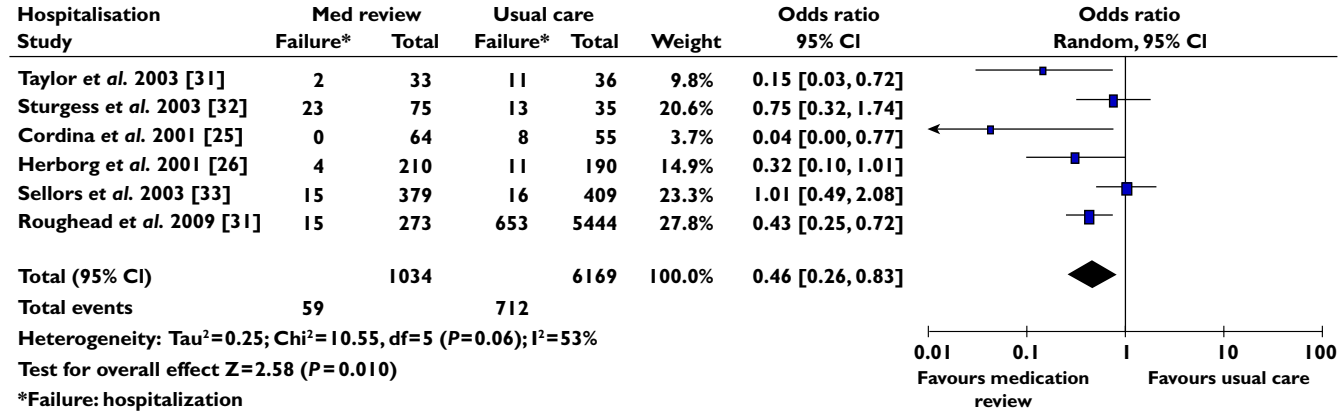


Figure 4

Forest plot of hospitalization outcome for studies with clinical medication review. OR is <1 when medication review reduced hospitalization

four RCTs and two non-RCTs. In the analysis of RCTs only, we find the same OR as in the combined (RCT and non-RCT) analysis. However the confidence interval increased and now included 1 (RCT only: OR 0.45, 95% CI 0.17, 1.23, $P = 0.12$) compared with (RCT and non-RCT: OR 0.46, 95% CI 0.26, 0.83, $P = 0.01$). The details of the subgroup analyses and publication bias assessment are available in Appendix S4.

Sensitivity analysis

Removal of any one study did not change the meta-analysis findings on blood pressure, mortality and the combined primary outcomes. Only the meta-analyses for LDL (no longer significant when Isset *et al*. [15] was removed, OR 2.68, 95% CI 0.88, 8.18, $P = 0.08$) and hospitalization (significant favouring the intervention group when

Table 4

Summary of reported findings of secondary outcomes

Secondary outcomes	Number of trials	Favour medication review	Favour usual care	No significant differences between the groups	Study reported both *significant and non-significant difference
Adherence	19	11	–	6	2
Economics	9				
Total medical costs	4	1	2	1	–
Total medication costs	6	1	2	3	–
Total cost for healthcare services	3	–	1	2	–
Quality of life	16				
All domains		3	–	8	–
Some domains†		3	2	–	–

*Outcomes were measured using two different tools, for example self-reported adherence and medication refill. Analysis with one tool may show a significant finding but the other one may not. †e.g. vitality (SF-36), energy/fatigue (HSQ) and mental summary (SF-36).

Holland *et al*. [16] was removed, OR 0.60, 95% CI 0.37, 0.95, $P = 0.03$) were affected by removing one study.

Secondary outcomes

Studies reporting secondary outcomes ($n = 32$) are summarized in Appendix S5. Nineteen studies reported improved adherence/compliance to medications as an outcome of their research. Of these, 12 provided clinical medication reviews (type 3), five studies were an adherence review (type 2) and two studies were a clinical medication review with prescribing (type 4). The majority of the studies ($n = 11$, 57.9%), eight clinical medication reviews and three adherence reviews, reported a significant improvement in adherence to medication as a result of pharmacists' interventions. Patients' quality of life was measured in 17 studies and nine studies measured the economic outcomes of the study. The findings for secondary outcomes are summarized in Table 4.

Discussion

This is the first study that has investigated the outcomes of a fee-for-service medication review. We excluded services provided at research and academic sites and/or were part of a trial. Studies on unfunded services that existed only as a part of a trial, while providing high quality information, may not reflect the reality of clinical practice. Pharmacists providing fee-for-service medication reviews will be subject to a number of limitations because of their responsibilities for many other aspects of the running of the pharmacy [8].

Our meta-analyses found that fee-for-service medication reviews by pharmacists performed as part of their daily practice resulted in some significant positive impacts on patients' clinical outcomes, primarily driven by the attainment of biomarker targets. Specifically they increased the number of patients achieving targets for blood pressure and LDL, but no clear effect was found on hospitalization or mortality rates. The outcome relating to blood pressure was found to have the lowest precision (OR 3.50, 95% CI 1.58, 7.75, $P = 0.002$) which we believe to be due to the small total sample size of the studies included. However, when all outcomes were pooled, the meta-analysis showed a statistically significant increase in the number of patients achieving the target clinical outcomes, reduced hospitalization and reduced mortality.

The magnitude of benefit seen in the present study is consistent with earlier meta-analyses on blood pressure [14, 17] and LDL outcomes [14, 18]. A meta-analysis of pharmacists' direct patient care interventions conducted in the USA found that systolic and diastolic blood pressure decreased by −7.8 mmHg (SD = 1.5, 95% CI −9.7, −5.8) and −2.9 mm Hg (SD = 0.7, 95% CI −3.8, −2.0), respectively [14]. In the same study, the mean difference of LDL reduction between pharmacists' interventions and the control group was −0.16 mmol l^{-1} (SD = 0.12, 95% CI −0.16, −0.17). Their study, however, did not differentiate the different types of medication review considered in our meta-analysis. It included all services with educational, behavioural and technical interventions, performed in all settings such as retail, in-patient, institutional and emergency department and was not focused on fee-for-service medication review in community settings [14]. Similar findings of a significant reduction in patients' systolic and diastolic blood pressure were also reported in a study focused on hypertension management [17]. Interventions included pharmacists' providing medication management, drug therapy monitoring and/or patient education and counselling at medical clinics and community pharmacies [17]. The magnitude of blood pressure reduction was −10.7 ± 11.6 mmHg in the intervention group and −3.2 mmHg ± 12.2 in the control group ($P = 0.047$) [17]. Interventions by pharmacists were also reported to lower patients' LDL con-

centration by –0.28 mmol l^{-1} (95% CI –0.44, –0.12 mmol l^{-1}) more than patients in the standard care group [18]. The scope of findings in these studies [17, 18], however, were limited to hypertension and dyslipidaemia and did not encompass evidence in other situations such as patients with asthma, with multiple medications or recently discharged from hospital.

We also evaluated the influence of different types of medication review on patients' outcomes which has not been considered previously. Our subgroup analysis showed that clinical medication review had positive impacts on blood pressure (OR 3.50, 95% CI 1.58, 7.75, P = 0.002) and LDL (OR 3.20, 95% CI 1.14, 8.98, P = 0.03). Furthermore, clinical medication review improved patient outcomes on hospitalization (OR 0.46, 95% CI 0.26, 0.83, P = 0.01) and this was not seen in an earlier systematic review with elderly patients, that did not separate the types of medication review [19]. A subgroup analysis on mortality for clinical medication review was not conducted as only one study reported this outcome. The odds ratio of achieving successful events in combined primary outcomes was increased, from 1.46 (95% CI 1.15, 1.84, P = 0.002) to 1.83 (95% CI 1.35, 2.49, P = 0.0001), when only studies with clinical medication review services were pooled. Adherence reviews did not show any statistically significant effects on hospitalization (OR 1.42, 95% CI 0.73, 2.78, P = 0.08), mortality (OR 1.92, 95% CI 0.79, 4.70, P = 0.15) or combined primary outcomes (OR 0.88, 95% CI 0.59, 1.32, P = 0.54).

These findings could be explained by the different focus of the types of medication review services compared. Clinical medication review (type 3) is perceived to be more comprehensive than an adherence review (type 2) as it promotes adherence in medication that has been assessed for its appropriateness, effectiveness and safety. An adherence review is founded on the assumption that the medication regimen is already optimal and focuses only on patient's problems with day-to-day use of medications.

Our study found that both clinical medication review (n = 8) and adherence review (n = 3) improved adherence to medications. We cannot confirm the impact of medication review on patients' quality of life as 50% (n = 8) of the studies showed no significant difference between the intervention and control group. Similarly, at least 85% of the studies in the systematic reviews by Chisholm-Burns *et al.* [14] and Machando *et al.* [17] reported non-significant differences in quality of life between the intervention and control group. However when the results on the general health dimension were pooled in a meta-analysis, the quality of life outcome was significant favouring pharmacists' intervention [14]. Whether the results can be generalized to pharmacists' services performed in the usual clinical setting, however, is unknown [14].

One limitation of the present study is that the analysis of 'combined primary outcomes' were conducted by combining different types of outcomes. Combining different outcomes is generally not suitable in meta-analyses as it may result in bias due to heterogeneity. However, since the goal of this study was to explore potential effects of different types of medication review services, the outcomes were pooled together to increase the power to see differences should a difference exist. To provide a basis for comparison outcomes were expressed as a change from baseline. Based on the exploratory nature and normalization of outcomes the decision to pool across outcomes was considered to be justified. We also note in our work that only published studies were included. However the use of Trim and Fill methods suggested that the impact of bias was unlikely to have a significant effect on the findings. Additionally, classification of types of medication review was based on the sometimes limited information available in the articles, and hence it is possible that the types of services may be mis-specified in some cases. However articles were independently reviewed and this effect is likely to be relatively minor. Nevertheless, care should be taken when interpreting the results of the subgroup analysis.

Conclusions

Fee-for-service pharmacist-led medication review services were shown to have a positive benefit on patient outcomes specifically on the attainment of clinical biomarkers. Furthermore services conducted as clinical medication reviews improved hospitalization, an important hard outcome for patients. Healthcare providers need to recognize the impact of different types of medication review on patients' outcomes. Further study specifically designed to compare the impact of different types of medication reviews is needed to quantify the importance of these findings.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1
Subject headings used to locate articles
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Summary of quality assessment criteria
Appendix S3
Summary of quality assessment for studies reporting primary outcomes
Appendix S4
Summary of subgroup analysis and publication bias assessment
Appendix S5
Summary of secondary outcomes reported in the studies included