Effects of pharmacist prescribing on patient outcomes in the hospital setting: a systematic review

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ABSTRACT

Objective: The objective of the review was to synthesize the best available evidence on the safety and effectiveness of pharmacist prescribing on patient outcomes in patients who present to hospital.

Introduction: Pharmacist prescribing is legal in many countries. Different models of prescribing include dependent, collaborative and independent. Existing reviews of pharmacist prescribing focus on studies in the community setting, or both community and hospital settings. Other reviews focus on descriptions of current practice or perspectives of clinicians and patients on the practice of pharmacist prescribing. A systematic review on the effects of pharmacist prescribing on patient outcomes in the hospital has not been previously undertaken and is important as this practice can help ease the burden on the healthcare system.

Inclusion criteria: Studies with controlled experimental designs comparing pharmacist prescribing to medical prescribing in the hospital setting were included in the review. Primary outcomes of interest included clinical outcomes such as therapeutic failure or benefit, adverse effects, and morbidity or mortality. Secondary outcomes included error rates in prescriptions, medication omissions on the medication chart, time or proportion of International Normalized Ratios in therapeutic range, time to reach therapeutic range, and patient satisfaction.

Methods: A comprehensive three-step search strategy was utilized. The search was conducted in January 2017 in eight major databases from database inception. Only studies in English were included. The recommended Joanna Briggs Institute approach to critical appraisal, study selection and data extraction was used. Narrative synthesis was performed due to heterogeneity of the studies included in the review.

Results: The 15 included studies related to dependent and collaborative prescribing models. In four studies that measured clinical outcomes, there was no difference in blood pressure management between pharmacists and doctors while patients of pharmacist prescribers had better cholesterol levels (mean difference in low density lipoprotein of 0.4 mmol/L in one study and 1.1 mmol/L in another; mean difference in total cholesterol of 1.0 mmol/L) and blood sugar levels (mean difference of fasting blood sugar levels of 15 mg/dL, mean difference of glycosylated hemoglobin of 2.6%). In two studies, pharmacists were better at adhering to warfarin dosing nomograms than doctors (average of 100% versus 62% compliance). In six studies, when prescribing warfarin according to dosing nomograms, equivalent numbers or more patients were maintained in therapeutic range by pharmacist prescribers compared to doctors. The incidence of adverse effects related to anticoagulant prescribing was similar across arms but all six studies were underpowered to detect this outcome. Three studies found that pharmacist prescribers made less prescribing errors (20 to 25 times less errors) and omissions (three to 116 times less omissions) than doctors when prescribing patients' usual medications on admission to hospital or in the preoperative setting. Two studies reported that patients were as satisfied with the services provided by pharmacist prescribers as with doctors.

Conclusions: This review provides low to moderate evidence that pharmacists can prescribe to the same standards as doctors. Pharmacists are better at adhering to dosing guidelines when prescribing by protocol and make significantly less prescribing errors when charting patients' usual medications on admission to hospital.

Keywords Drug prescription; hospital; pharmacist; prescribing; review

JBI Database System Rev Implement Rep 2018; 16(9):1823–1873.

Summary of Findings

Effects of pharmacist prescribing on patient outcomes in the hospital setting

Bibliography: Poh EW, McArthur A, Stephenson M, Roughead EE. Effects of pharmacist prescribing on patient outcomes in the hospital setting: a systematic review. JBI Database System Rev Implement Rep 2018; 16(9):1823–73.

Outcome	Impact/effect	Number of participants (studies)	Certainty
Therapeutic failure or benefit – cardiovascular disease assessed with: Blood pressure control follow-up: range 6 months to 29 months	Pharmacists were just as effective as doctors in prescribing medications for blood pressure control. *Mean change in systolic blood pressure from baseline was +2 mmHg and -2 mmHg in the intervention and control arm respectively in one study (excluding two studies that did not account for patient mix).*	846 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c,d,e]
Therapeutic failure or benefit – cardiovascular disease assessed with: Diabetes (blood sugar) control follow-up: range 12 months to 29 months	Pharmacists were just as effective as doctors in prescribing medications for blood sugar control. *Two studies reported a reduction in mean change from baseline in the intervention arm compared to the control arm: -8 mg/dL versus +7 mg/dL (fasting blood sugar levels) in one study and -1.8 % versus -0.8 % (glycosylated haemoglobin) in another study.*	793 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c,d,e]
Therapeutic failure or benefit – cardiovascular disease assessed with: Cholesterol control follow-up: range 6 months to 12 months	Pharmacists were just as effective as doctors in prescribing medications for cholesterol control. *Two studies reported a reduction in mean change from baseline in the intervention arm compared to the control arm for low density lipoprotein: -0.7 mmol/L versus -0.3 mmol/L mmol/L in one study and -1.3 mmol/L versus -0.2 mmol/L in another. One study reported a reduction in mean change from baseline in the intervention arm compared to the control arm for total cholesterol: -1.1 mmol/L versus -0.1 mmol/L.*	178 (2 RCTs)	⊕⊕◯◯ LOW [b,c,e]
Prescribing errors assessed with: Medication prescribing errors and medications omitted from chart	Pharmacist prescribing of patients' usual medications on admission to hospital or in the preadmission clinic reduced prescribing error rates and the omission of medications from medication charts. *Average number of prescribing errors was 4.5 (range 2 – 7) in the intervention arm and 113.5 (range 51 – 176) in the control arm (two studies). Average number of medication omissions was 11.5 (range 11 – 12) in the intervention arm and 890 (range 383 – 1397) in the control arm (two studies).*	1486 (3 RCTs)	⊕⊕⊕◯ MODERATE [c,f]
Adverse effects related to anticoagulant therapy assessed with: Bleeding or thromboembolic events	Pharmacists were just as effective as doctors in prescribing anticoagulants according to dosing nomograms, with little or no difference in adverse effect events. *The number of events between arms were similar in all studies, but these studies were underpowered and a meaningful conclusion cannot be drawn.*	901 (6 RCTs)	⊕⊕◯◯ LOW [e,f,g]

Appropriate warfarin doses prescribed assessed with: Accordance to warfarin nomogram	Pharmacist prescribing of warfarin improved adherence to dosing nomograms. *On average, pharmacist prescribers complied with dosing nomograms 100% of the time compared to doctors who complied 62% (range 46% - 73%) of the time.*	117 (2 RCTs)	⊕⊕◯◯ VERY LOW [c,e,f]
Effectiveness of anticoagulation prescribing assessed with: International Normalized Ratio control	Pharmacist prescribing of warfarin improved patient-time spent in therapeutic range. *Patient-time, percentage of patients or International Normalized Ratio in therapeutic range ranged from 57% – 78% in the intervention arm compared to 18% – 79% in the control arm.*	958 (6 RCTs)	⊕⊕◯◯ VERY LOW [d,e,f]

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No allocation concealment or unable to be established

b. Unable to establish if outcome assessors blinded

c. Participants or those delivering treatment not blinded

d. Used surrogate outcomes but the surrogate marker is well established as a marker for morbidity or mortality; evidence level not downgraded

e. Small number of participants

f. Includes quasi experimental trials and may be affected by allocation bias

g. Small number of events

Introduction

For conditions that can be medically managed, diagnosis is often followed by prescribing medications to treat the condition or alleviate symptoms associated with the condition. Traditionally, the act of prescribing has been associated with medical practitioners. Non-medical prescribing is the extension of prescribing rights to other specified professions, including nurses, pharmacists, optometrists and podiatrists. It was originally introduced to allow a more flexible system for the prescribing, supply and administration of medications in order to help improve patients' access to medications and ease the workload burden on general practitioners.[1,2] Nurse prescribing was first introduced in the United States of America (USA) in 1969.[3] In the last two decades, legislation changes have also occurred in various countries around the world to allow for non-medical prescribing.[3-5] Pharmacist prescribing is currently legal in Canada, New Zealand, the United Kingdom (UK) and the USA.[2,6] In the UK, a limited prescribing right was introduced in 2003, followed by independent prescribing in 2006.[7]
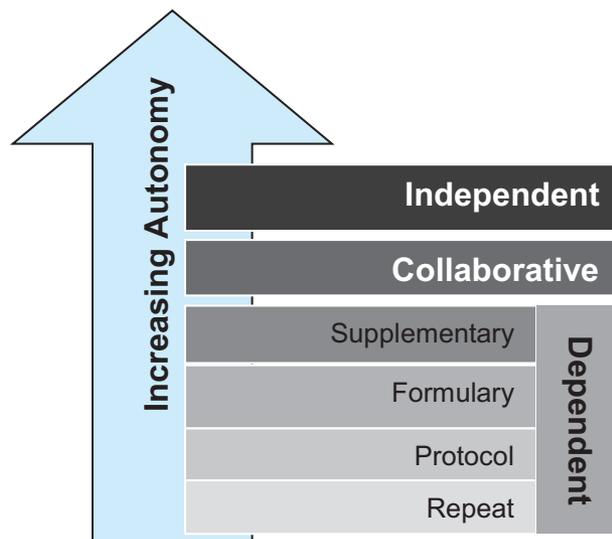
Different models of pharmacist prescribing have been described in the literature.[1,5,6] For the purposes of this review, the types of pharmacist prescribing have been defined as independent, collaborative and dependent. In independent prescribing, pharmacists have the greatest autonomy in prescribing medications and are responsible for the assessment, diagnosis and clinical management of patients. In collaborative prescribing, there is a cooperative practice relationship between the pharmacist and doctor. The doctor diagnoses and makes initial treatment decisions for the patient while the pharmacist selects, monitors, modifies, continues or discontinues the treatment as appropriate. Dependent prescribing places more restrictions on the non-medical prescriber by limiting medication prescription according to protocols or formularies. The different types of dependent prescribing include prescribing by protocol, prescribing by formulary, repeat prescribing and supplementary prescribing. In prescribing by protocol, a written guideline (protocol) describes in explicit detail the activities that may be performed by the non-medical practitioner. The protocol includes a limited list of the diseases and

medication classes which the practitioner may prescribe. The protocol may also list medications in preferential order, along with suggested doses and provide recommendations on when dose modification should be considered. Detailed protocols also contain additional clinical information such as laboratory tests (e.g. renal function) or diagnostic tests (e.g. blood pressure monitoring) that should be performed for the patient. In prescribing by formulary, non-medical prescribers may prescribe from a predefined list of medications for specific medical conditions. Medications not on the list may not be prescribed. Repeat prescribing is a medication-refill service where pharmacists in clinics prescribe for patients who require continuing prescriptions prior to their next available appointment with their doctor. In supplementary prescribing, a voluntary partnership between the doctor and pharmacist exists, where the doctor undertakes the initial assessment and the pharmacist prescribes in accordance with the doctor's documented care plan. The care plan clearly outlines the therapeutic options agreed upon by the doctor and patient.

Figure 1 depicts the relative autonomy of pharmacists for the prescribing models described above.

Systematic reviews on non-medical prescribing, specifically nurse prescribing, are available in the literature.[8,9] Other reviews of non-medical prescribing are also available but do not focus exclusively on pharmacist prescribing in the hospital setting. For example, a review published in 2011 assessed the contribution of prescribing by nurses and allied health professionals, but was limited to the primary care setting.[3] A more recent review published in 2016 reported on non-medical prescribing in both primary and secondary care settings, but presented combined results for all allied health professionals, including pharmacist prescribers.[10] In 2004, a review focusing on pharmacist prescribing was published, and included prescribing in both the community and hospital setting.[11] This review identified only four studies with an experimental design and concluded that additional research was needed to establish the validity of pharmacist prescribing. In a review which evaluated the impact of pharmacists in the area of mental health, some studies involving pharmacist prescribing were included but these studies were not the main focus of the review.[12] Other published reviews which have included pharmacist prescribing mainly relate to descriptions of the practice (including existing policies and procedures) in a specific country or region, barriers to successful implementation, or the perspectives of pharmacist prescribers, other healthcare professionals or patients on pharmacist prescribing.[2,6,13] A systematic review on the effects of pharmacist prescribing on patient outcomes in the hospital setting is therefore warranted as it is important to inform health policy-makers on the safety and effectiveness of this intervention in easing the burden on the healthcare system. The current review was conducted according to an *a priori* published protocol.[14]

Figure 1: Relative autonomy of pharmacist prescribing models

Review question/objective

The objective of this review was to determine the effects of pharmacist prescribing in the hospital setting.

More specifically, the objectives were to synthesize the best available evidence on the safety and effectiveness of pharmacist prescribing by using doctor prescribing as the comparator. Outcomes of interest were related to patient outcomes in the hospital setting, where patients were either inpatients or outpatients.

Inclusion criteria
Participants

This review considered studies that included patients in a hospital setting, including those admitted to hospital, those being assessed prior to elective admission, and those being assessed in outpatient clinics. Children and adults of all ages (i.e. from neonates to geriatrics), not limited to any specific medical condition or admission reason, who were prescribed medication(s) by a pharmacist, were included in this review.

Studies conducted in settings other than hospitals such as specialist medical centers, health maintenance organizations or community clinics were not included in this review. In addition, studies that combined data from a hospital with a primary care setting were excluded from the review.

Intervention

This review considered studies that evaluated all forms of pharmacist prescribing in the hospital setting.

Studies were not considered to meet the inclusion criteria in cases where the pharmacist transcribed from one prescription to another, and a doctor review and signature were still required on the transcribed prescription before the order was considered legitimate.

Comparator

This review considered studies that compared the intervention to usual care, i.e. prescriptions by hospital doctors. Studies that did not have a comparator group were excluded from the review.

Outcomes

This review considered any study that reported the effects of pharmacist prescribing on patient outcomes.

The primary outcome included any of the following reported clinical outcomes:
- Therapeutic failure or benefit, i.e. the effectiveness of medications prescribed to control specific disease states, specifically blood pressure, diabetes and cholesterol, measured as a change in baseline parameters or the difference between arms.
- Number of adverse events related to medications prescribed, i.e. bleeding or thromboembolic events.
- The incidence of morbidity or mortality related to medication prescribing.

Secondary outcomes included any of the following:
- Error rates in prescription, specifically incorrect medication choice, dose, frequency or unnecessary medication. Errors were measured by comparison to medication histories taken by a pharmacist or by comparison to agreed protocols or guidelines.
- Errors of omission due to omission of medication from the medication chart and the clinical significance of the omission. Errors of omission were measured by comparison of the medication chart to a patient's medication history taken by a pharmacist on admission to hospital while the clinical significance of the omission was assessed by an independent panel.
- Requirement for change in prescription by the doctor following prescribing by the pharmacist.
- Appropriate dose selection for medications prescribed, where doses were considered appropriate when prescribed according to the patient's medication history or an agreed protocol or guideline.
- Time or proportion of International Normalized Ratios (INRs) in therapeutic range.
- Time to reach therapeutic range.
- Patient satisfaction, measured using patient satisfaction surveys.

Types of studies

This review considered any study with a controlled experimental design for inclusion, i.e. randomized controlled trials (RCTs) and quasi experimental prospectively controlled trials.

Studies with a qualitative design, publications not pertaining to primary research or papers published in languages apart from English were excluded from the review. Studies with lower levels of evidence, such as non-controlled quasi experimental trials or observational studies (analytic or descriptive) were excluded as sufficient numbers of RCTs or prospectively controlled quasi experimental trials were identified.

Studies published from database inception up until January 24, 2017 were considered for inclusion in this review. Studies were retrieved from time of database inception to ensure that all possible

relevant studies were included as there is variation in the dates that pharmacist prescribing was introduced in different countries.

Methods

Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilized in this review. An initial limited search of MEDLINE (OVID platform) and CINAHL was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. This informed the development of a search strategy which was tailored for each information source. Full search strategies for the databases are detailed in Appendix I.

A second search using all identified keywords and index terms was then undertaken across all included databases on January 24, 2017. A combination of MeSH and keywords was used; text variations were set out clearly in a logic grid to enable replicability of the search results.

Thirdly, the reference lists of all studies selected for critical appraisal were screened for additional studies. Scopus was used to identify other published studies that cited the papers being considered for inclusion in the review; these studies were assessed for eligibility against the inclusion criteria.

Information sources

The databases searched included CINAHL, Cochrane Register of Controlled Trials (CENTRAL), Embase, PubMed, Scopus and Web of Science Core Collection.

The search for unpublished studies was performed using Google and MedNar.

Study selection

Following the search, all identified citations were collated and uploaded into Endnote and duplicates removed. Titles and abstracts were screened by the main reviewer for relevance to the review topic. Where required, the full text of the article was appraised to determine if it met the inclusion criteria as listed above. Studies that met the inclusion criteria were imported into the Joanna Briggs Institute System for Unified Management, Assessment and Review of Information (JBI SUMARI).[15] Full-text studies that did not meet the inclusion criteria were excluded and reasons for exclusion are provided in Appendix II.

Assessment of methodological quality

Selected studies were critically appraised by two independent reviewers at the study level for methodological quality in the review using the standardized critical appraisal instruments from Joanna Briggs Institute for the following study types: RCTs[16] and quasi experimental studies.[16] Any disagreements that arose were resolved through discussion or with a third reviewer. In some instances, the issue was also discussed with a fourth reviewer, usually when clarification or contextualization of the questions in the critical appraisal instruments were required.

Following critical appraisal, studies that did not meet a certain quality threshold were excluded. At a minimum, all studies required seven "yes" responses to the questions listed in the critical appraisal tools. Two "yes" responses were required for the following questions and could be part of the seven "yes" responses: Question 7 ("Were treatment groups treated identically other than the intervention of interest?") and Question 10 ("Were outcomes measured in the same way for treatment groups?") for RCTs, and Question 4 ("Was there a control group?") and Question 7 ("Were the outcomes of participants included in any comparisons measured in the same way?") for quasi experimental studies.

Data extraction

Data was extracted from papers included in the review using the standardized data extraction tool available in Joanna Briggs Institute System for Unified Management, Assessment and Review of Information (JBI SUMARI).[16] The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Statistical meta-analysis was not possible due to heterogeneity between studies and therefore the findings were presented in narrative form including tables and figures to aid in data presentation where appropriate.

Assessing certainty in the findings

A Summary of Findings was created using GRADE-Pro GDT software.[17] The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach for grading the quality of evidence was followed.[18] The Summary of Findings ranks the quality of the evidence based on study

limitations (risk of bias), indirectness, inconsistency, imprecision and publication bias.

The following outcomes were included in the Summary of Findings:

- Therapeutic failure or benefit
- Prescribing errors
- Adverse events related to therapy
- Appropriateness of doses prescribed
- Effectiveness of anticoagulant prescribing.

Results

Study inclusion

From the systematic search of the eight databases, reference lists of selected studies considered for inclusion and papers which cited selected studies considered for inclusion, a total of 22,352 articles were identified for screening (excluding duplicates). Following screening of the title and abstract of the articles, 66 papers were retrieved for full-text review. Of this number, 50 articles were excluded from the review based on the specified inclusion and exclusion criteria. Refer to Appendix II for the complete list of excluded studies and reasons for their exclusion. The 16 remaining articles were assessed for methodological quality and were all found to be suitable for inclusion in the review. A summary of the studies included in this review is presented in Appendix III.

The results of the search are presented in a PRISMA flow diagram (Figure 2).
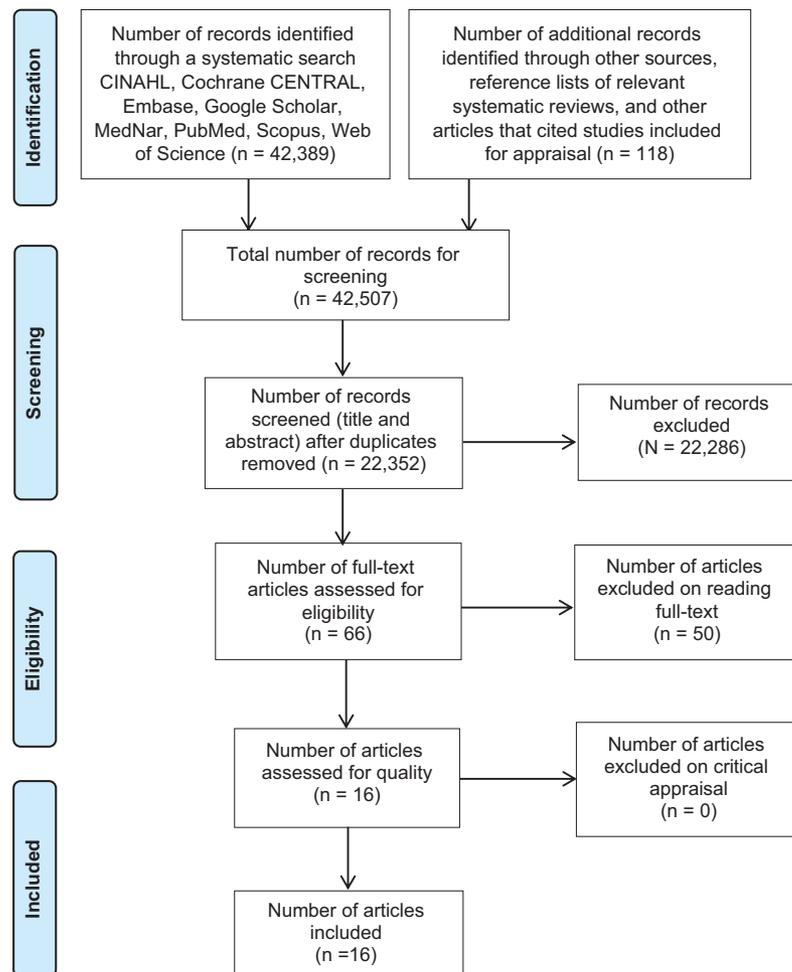
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

Figure 2: PRISMA flow diagram of search and study selection process

Methodological quality

The results for the critical appraisal of RCTs are presented in Table 1. In the nine papers which comprised eight RCTs, three did not specify the method of randomization used.[22,23,26] Of the remaining five studies, four used a computer generated randomized list,[19,21,24,25] and one used random numbers prepared by a clinical trials pharmacist.[27] Allocation to treatment groups was reported to be concealed in three studies (two papers) out of nine, leading to the potential for distortion of the implementation of the allocation process indicated by randomization.[19,20,25,27] Treatment groups were deemed to be similar at baseline in three studies.[22,24,25] In the remaining six studies, baseline characteristics differed in terms of gender (more males in the control group),[21] age (higher mean age in control group),[19,27] number of medications on admission,[19,20] baseline diastolic blood pressure (higher in intervention group),[26] and baseline fasting blood sugar levels (higher in intervention group).[23] These differences in baseline may indicate a risk of selection bias, which confers a risk that the measured effect between groups is not solely attributed to the intervention. There were two papers (one study) where it was possible to blind participants to treatment assignment.[19,20] This occurred in a preoperative assessment clinic where patients saw the same four health professionals prior to elective surgery.

Blinding is not possible or very difficult to implement in clinical settings due to the nature of the intervention, i.e. pharmacist prescribing, especially in cases where patients presented to an outpatient clinic for review by a pharmacist. There were no studies where those delivering treatment were blind to treatment assignment. Again, this is not possible due to the nature of the intervention. For example, a nurse administering medication treatment is easily able to determine whether a pharmacist or doctor has prescribed the medication order. However, this is not likely to affect the outcome of the study as nursing staff would not have the autonomy to change medication orders and medication therapy is administered as ordered by prescriber (whether it is a pharmacist or a doctor).

Two studies (three papers) had outcome assessors that were blind to treatment assessment.[19,20,25] In most studies, the outcome assessor was not specified, increasing the risk of bias in the measurement of outcomes if this had been performed by the investigator of the study. Question 7 ("Were treatment groups treated identically other than the intervention of interest?") was scored a "yes" provided any

Table 1: Assessment of methodological quality of randomized controlled trials

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total
Hale et al.[19]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	11/13
Hale et al.[20]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	11/13
Chan et al.[21]	Y	U	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	8/13
Chenella et al.[22]	U	U	Y	U	U	U	Y	U	Y	Y	Y	Y	Y	7/13
Hawkins et al.[23]	U	U	N	N	N	U	Y	Y	Y	Y	Y	Y	Y	7/13
Jacobs et al.[24]	Y	N	Y	N	N	U	Y	Y	Y	Y	Y	Y	Y	9/13
Marotti et al.[25]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	U	Y	9/13
Vivian[26]	U	U	N	N	N	U	Y	Y	Y	Y	Y	Y	Y	7/13
Weeks and Fyfe[27]	Y	Y	N	N	N	U	Y	Y	Y	Y	Y	N/A	Y	8/12
%	67	44	33	22	0	33	100	89	100	100	89	78	100	

N: No, N/A: Not applicable, U: Unclear, Y: Yes. Values are indicative of Y (Yes) responses.
JBI critical appraisal checklist for randomized controlled trials: Q1: Was true randomization used for assignment of participants to treatment groups?; Q2: Was allocation to treatment groups concealed?; Q3: Were treatment groups similar at the baseline?; Q4: Were participants blind to treatment assignment?; Q5: Were those delivering treatment blind to treatment assignment?; Q6: Were outcomes assessors blind to treatment assignment?; Q7: Were treatments groups treated identically other than the intervention of interest?; Q8: Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?; Q9: Were participants analysed in the groups to which they were randomized?; Q10: Were outcomes measured in the same way for treatment groups?; Q11: Were outcomes measured in a reliable way?; Q12: Was appropriate statistical analysis used?; Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

differences in treatment between groups were considered part of the intervention. For example, the intervention was considered identical between groups in the case of warfarin prescribing where pharmacists used warfarin nomograms but doctors did not. Similarly the intervention was also considered identical if the follow-up period or clinic appointments varied between doctors and pharmacist prescribers. The remaining questions in the appraisal checklist (Q8 to Q13) scored positively in 78% of cases or above, reflecting good study methodology for follow-up, measures of outcome, statistical analysis and trial design.

The results for the critical appraisal for quasi experimental trials are presented in Table 2. All seven quasi experimental trials included in this review had a clear "cause" and "effect" that was being measured and a control group, and they measured the same outcome measures reliably. Participants were deemed similar between groups in three studies.[28,32,34] Patient demographics were not reported in two studies,[30,31] and reported only for age in one study.[29] For the remaining study, participants were older in the intervention group.[33] Question 5 ("Were there multiple measurements of the outcome both pre and post the intervention/ exposure?") scored "yes" in cases where multiple INR measurements were taken, even though these INR results were used to calculate one single outcome measure (e.g. proportion of INRs within

therapeutic range). Four studies performed statistical analysis on the outcomes measured. Two studies did not calculate statistical significance and one did not specify the method which was used.

Characteristics of included studies

The 16 articles included in this review related to 15 studies. Hale et al.[20] reported on a subset analysis of the study by Hale et al.[19]

Of the 15 included studies, eight were RCTs,[19,21-27] and six were prospectively controlled quasi experimental studies.[28-33] In one study, the intervention was studied prospectively, but patients in the concurrent control group were identified retrospectively and data obtained through chart reviews.[34] This study was still considered suitable for inclusion as retrospective data collection for the control group was deemed unlikely to affect the outcome of the study as usual care remained unchanged. The studies were conducted in five countries including Hong Kong,[21] Canada,[34] United Kingdom,[28,29] Australia,[19,25,27,33] and the USA,[22-24,26,30-32] with publication dates ranging from 1979 to 2016.

Seven of the studies recruited less than a hundred participants (range 14 – 81),[22,26,27,29-31,34] while the remaining eight studies recruited between 137 to 881 participants.[19,21,23-25,28,32,33]

The studies were carried out in the following hospital settings: patients admitted to hospital,[22,28-34] outpatient clinics,[21,23,24,26,27] and preoperative/preadmission clinics.[19,25] Participants were

Table 2: Assessment of methodological quality of prospectively controlled quasi experimental trials

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total
Boddy[28]	Y	Y	Y	Y	Y	U	Y	Y	Y	8/9
Burns[29]	Y	U	Y	Y	Y	U	Y	Y	Y	7/9
Damaske and Baird[30]	Y	U	Y	Y	Y	Y	Y	Y	N/A	7/8
Pawloski and Kersh[31]	Y	U	Y	Y	Y	Y	Y	Y	U	7/9
Schillig et al.[32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/9
Tong et al.[33]	Y	N	Y	Y	N	Y	Y	Y	Y	7/9
Chau et al.[34]	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8/8
%	100	43	100	100	86	71	100	100	57	

N: No, N/A: Not applicable, U: Unclear, Y: Yes. Values are indicative of Y (Yes) responses.
JBI critical appraisal checklist for quasi experimental studies: Q1: Is it clear in the study what is the "cause" and what is the "effect" (i.e. there is no confusion about which variable comes first)?; Q2: Were the participants included in any comparisons similar?; Q3: Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?; Q4: Was there a control group?; Q5: Was there multiple measurements of the outcome/ conditions both pre and post the intervention/exposure?; Q6: Was follow-up complete, and if not, was follow-up adequately reported and strategies to deal with loss to follow-up employed?; Q7: Were the outcomes of participants included in any comparisons measured in the same way?; Q8: Were outcomes measured in a reliable way?; Q9: Was appropriate statistical analysis used?

adults (over 18 years) in 13 studies; age was not reported in the remaining two studies, but participants were likely to be adults based on their co-morbidities or reason for admission.[30,31] Racial profile was reported in five studies, where participants were all Chinese,[21] mostly Mexican American,[23] mostly African American[26] or mostly Caucasian.[4,32]

The model of pharmacist prescribing used in the studies included prescribing by protocol,[21,22,26,28-31,34] supplementary prescribing,[19,24,25,33] and collaborative prescribing.[23,27] In the remaining study, the model of prescribing used was unclear.[32]

Pharmacists prescribed a range of medications including anticoagulants (heparin, warfarin, venous thromboembolism prophylaxis in surgical patients),[19,21,22,28-32,34] antihypertensive medications,[23,24,26] antidiabetic medications,[23,24] and medications for hypercholesterolemia.[24,27] In three studies, pharmacists were not restricted to prescribing any particular class or type of medication.[19,25,33]

In all studies, pharmacists were prescribing autonomously either according to available guidelines, clinical judgement or following discussion with a doctor. In one study, counter signature of prescriptions by a doctor was a site requirement, which meant that all patients in the intervention arm were seen by the pharmacist before the doctor.[19] In another study, all patient care assessments and plans made by the pharmacist were subsequently reviewed by doctor auditors (not involved in the care of any patients in the study) to assure provision of adequate medical care to patients.[23] The authors of this study reported that plans made by the pharmacist were rarely changed by the auditors.

In most of the included studies, guidelines or dosing nomograms were available to guide the pharmacist in the prescribing of medications.

A warfarin dosing nomogram was used by pharmacists in five studies to adjust the warfarin dose.[21,28-30,34] In one of these five studies, dosing nomograms were not used by doctors.[34] In one study, the pharmacist prescriber could deviate from the dosing nomogram if it was deemed necessary according to their clinical judgement.[30] In the remaining studies, dosing nomograms were either not used,[22] or it was unclear if one was available.[32]

In the two studies where heparin was prescribed, a protocol for dosage adjustment was available for both pharmacists and doctors in one study;[22] in the other study a heparin protocol was used by pharmacist prescribers but was not mandatory for doctors.[31]

In one study, venous thromboembolism prophylaxis for elective surgery patients was prescribed according to local and national guidelines, in addition to a risk and contraindication assessment.[19]

In one study, medications for blood sugar, blood pressure and lipid control were prescribed in an outpatient setting according to most recent guidelines and clinical trial evidence.[24]

In the remaining studies, pharmacist prescribing was based on one of the following: protocols which advised on the types of medications which should be withheld, depending on the nature of the surgical procedure;[25] according to national guidelines (sixth report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure);[35] statin (HMG-CoA reductase inhibitor) dose adjustment and monitoring algorithm;[27] or an agreed plan following discussion with the doctor.[31] All studies included in the review compared pharmacist prescribing to usual care, i.e. prescribing by doctors. In some studies, the level of experience of the clinicians (pharmacists and doctors) in the two arms varied; e.g. an experienced clinical pharmacist versus a junior doctor.[28,29] In most other studies where the qualification of the doctor was specified, they were at a consultant level and specialized in a particular field of medicine.[21-23,26,30,31,34] The experience level of the pharmacist ranged from clinical pharmacists (generalists or otherwise unspecified),[19-21,23,25,27,30,31,33] those who specialized in a particular field (e.g. hematology, anticoagulation clinic),[22,26,28,29,32,34] to pharmacists with postgraduate residency training.[24,32]

The outcomes measured in the included studies varied depending on the type of medications that were being prescribed by the pharmacist.

Primary outcome measures included:
- Therapeutic failure or benefit with regards to blood pressure control, diabetes control, cholesterol control.[23,24,26,27]
- Adverse events associated with warfarin or heparin prescribing (bleeding or thromboembolic events, death).[21,22,29,30,32,34]

Secondary outcome measures included:
- Prescription errors including medication omissions and the clinical significance of the error, incorrect doses, incorrect frequencies, incorrect or unnecessary medication.[19,20,25,33]

- Requirement for change in prescription by medical prescriber following prescribing by pharmacist.[19]
- Appropriate prescribing of venous thromboembolism prophylaxis in patients being admitted for elective surgery.[19]
- For warfarin or heparin prescribing:
  - Appropriate loading and maintenance doses of warfarin prescribed.[29,30]
  - Number of patients, patient time or proportion of INRs in, under or over therapeutic range.[21,28-30,32,34]
  - Time to reach therapeutic range.[22,29-31,34]
- Patient satisfaction.[21,26]

Review findings

The major findings of this review are reported under five broad categories: therapeutic failure or benefit, adverse events related to therapy, appropriateness of prescriptions and prescribing errors, anticoagulant prescribing (INR control and time to therapeutic range) and patient satisfaction.

Therapeutic failure or benefit

Clinical effectiveness of medication therapy was measured in four RCTs.[23,24,26,27] The outcome measures included systolic blood pressure (SBP), diastolic blood pressure (DBP), blood sugar levels (BSLs), glycosylated hemoglobin (HbA1c), low density lipoprotein (LDL) cholesterol and total cholesterol (TC).

In Hawkins et al.,[23] there was a lower proportion of patients with hypertension only (p $\leq$ 0.04), a higher proportion of patients with both diabetes and hypertension (p $\leq$ 0.025), and higher body mass index values (p $<$ 0.05) in the intervention group when compared to the control group.

In Jacobs et al.,[24] the main inclusion criteria was based on HbA1c and not all patients had a clinical diagnosis of hypertension at baseline. A similar number of patients in both groups had a diagnosis of hypertension or dyslipidemia. Pre-trial and post-trial measurements of blood pressure, HbA1c and LDL cholesterol were made at baseline and six and 12 months ($+/-$ one month) of the study period. For the purposes of this review, only observations at the 12-month period are discussed in detail to ensure maximum benefit of medication therapy had been achieved at the time the endpoint was measured.

Vivian[26] recruited a lower percentage of patients with diabetes (42% versus 59%) and a lower percentage of smokers (15% versus 26%) in the intervention group compared to the control group.

In Weeks and Fyfe,[27] patients were seen by the pharmacist every six weeks and were provided with lifestyle advice at each visit. It is unclear if patients in the doctor group were also provided with advice on non-medication measures to reduce cholesterol at each visit.

Blood pressure control

Three studies measured blood pressure control to evaluate the effect of pharmacist prescribing on the outcomes of patient care.[23,24,26] Participants were all male and mostly African-American in one study,[26] mainly Mexican-American in another,[23] and mainly Caucasian in the remaining study.[24] Due to heterogeneity in study methodology (analytical method) and population, no meta-analysis was performed. A narrative description of the studies follows.

In all three studies, the difference in means of post-test assessment between the two groups was used to measure the significance of the difference between arms. In two studies, there was a significant difference in baseline blood pressure for either SBP or DBP between the intervention and control group.[24,26] This was not adjusted for the analysis, thus the outcome analysis using difference in means of post-test blood pressure may be inaccurate.

One study also calculated the significance of the change in mean blood pressure from baseline for both groups.[26] In this study, the mean SBP change from baseline, which was reported narratively, differed slightly from that which can be calculated from the pre-trial and post-trial data presented in the paper, and is reflected in Table 3. Mean SBP and mean DBP changes from baseline were also presented in the table but statistical significance could not be calculated as there were insufficient data presented in the papers.

Two studies also reported on the number of patients who achieved target blood pressure at the end of the study.[24,26]

Results for mean SBP and DBP measured are summarized in Table 3.

In Hawkins et al.,[23] there was an increase in post-trial mean SBP from baseline in the intervention

Table 3: Pre-test and post-test systolic blood pressure and diastolic blood pressure

Systolic blood pressure (SBP)					Mean SBP change from baseline	
Study details	Intervention Mean SBP (mmHg)		Control Mean SBP (mmHg)		Intervention (mmHg)	Control (mmHg)
	Pre-trial	Post-trial	Pre-trial	Post-trial		
Hawkins et al.[23] RCT	145 +/− 15	147 +/− 18	143 +/−14	141 +/− 13	+2	−2
	Pre-trial: Not statistically significant Post-trial: p ≤ 0.001, t = 3.88					
Jacobs et al.[24] RCT	142.5 +/− 15.2	132.5 +/− 16.3	134.8 +/− 16.9	135.4 +/− 14	−10	+0.6
	Pre-trial: p = 0.03 Post-trial: p = 0.223					
Vivian[26] RCT	149.0 +/− 15.3	130.5 +/− 13.2	152.8 +/− 14.3	148.4 +/− 21	−18.4 (95% CI, −26.3, −10.5)	−3.98 (95% CI, −11.8, 3.79)
	Pre-trial: p = 0.252 Post-trial: p = 0.0002				p = 0.01	
Diastolic blood pressure (DBP)					Mean DBP change from baseline	
Study details	Intervention Mean DBP (mmHg)		Control Mean DBP (mmHg)		Intervention (mmHg)	Control (mmHg)
	Pre-trial	Post-trial	Pre-trial	Post-trial		
Hawkins et al.[23] RCT	86 +/− 6	84 +/− 6	86 +/− 6	84 +/− 4	−2	−2
	Pre-trial and post-trial values not statistically significant					
Jacobs et al.[24] RCT	79.4 +/− 9.9	72.0 +/− 8.5	78.3 +/− 10.4	77.6 +/− 8.4	−7.4	−0.7
	Pre-trial: p = 0.493 Post-trial: p = 0.001					
Vivian[26] RCT	89.8 +/− 10.9	77.5 +/− 10.7	77.9 +/− 11.9	80.4 +/− 11.4	−12.3 (95% CI, −16.49, −8.28)	+2.5 (95% CI, −1.49, 6.57)
	Pre-trial: p = 0.0012 Post-trial: p = 0.259				p = 0.001	

CI: confidence interval, DBP: diastolic blood pressure, RCT: randomized controlled trial, SBP: systolic blood pressure.

group, which was statistically significant (p ≤ 0.001). This was in direct contradiction to the goal of blood pressure reduction in this study. There were no statistically significant differences between pre-trial and post-trial DBP. It is possible that the increase in SBP in the intervention group could be due to the higher number of patients who had both hypertension and diabetes compared to the control group. A subgroup analysis was not conducted by the investigators to assess the difference in study participants between the two groups and therefore these results should be interpreted with caution.

In the study by Jacobs et al.,[24] there was a significant difference in the pre-trial mean SBP between both groups, with baseline mean SBP higher in the intervention group (p = 0.03). There was also a higher proportion of patients in the intervention group who were smokers, had a family history of premature heart disease, hypertension, coronary heart disease and dyslipidemia which may account for the higher baseline SBP, although these differences did not reach statistical significance. Post-trial SBP was not found to be significantly different between groups (p = 0.223). As not all patients had a clinical diagnosis of hypertension at baseline, the findings that patients in the intervention arm had a mean SBP reduction of 10 mmHg compared to an increase of 0.6 mmHg in the control arm is not surprising, as more patients in the control arm were closer to being normotensive at baseline. There was a significant reduction in post-trial mean DBP in the intervention group compared to the control group (p = 0.001). Differences in patient characteristics between groups were not adjusted

for the outcome analysis, thus adjusted effects were not reported.

The study by Vivian[26] found post-trial SBP in the intervention group was significantly lower compared to the control group (p = 0.0002). For DBP, there was a significant difference in baseline mean between groups, with mean DBP higher in the intervention group (p = 0.0012); the reason for this difference is unclear. Post-trial, no significant differences in DBP were found between arms (p = 0.259). A separate analysis was conducted for patients with diabetes but as diabetic patients accounted for approximately 50% of the total participants, these results reflected the overall study findings. The results were not adjusted for patient mix.

In the outcome analysis conducted by Vivian,[26] mean changes in SBP and DBP from baseline for both groups were also compared. Mean SBP decreased by 18.4 mmHg in the intervention group compared to 3.98 mmHg in the control group, a finding that was statistically significant (p = 0.01). Mean DBP decreased by 12.38 mmHg in the intervention group compared to an increase of 2.54 mmHg in the control group, a finding that was also statistically significant (p = 0.001).

Two studies reported patient numbers achieving a predefined target blood pressure. The study by Vivian,[26] which recruited patients with hypertension with or without diabetes, used target blood pressure of 140/90 mmHg. The number of patients who achieved this target was 21 (81%) in the intervention group and eight (30%) in the control group, a finding that was statistically significant (p = 0.001). The study by Jacobs et al.[24] which recruited patients with type 2 diabetes had a lower target blood pressure of equal to or below 130/80 mmHg. The study found that at 12 months, target SBP was met in 29 patients (51%) in the intervention group and 30 patients (43%) in the control group, while target DBP was met in 48 patients (84%) in the intervention group and 54 patients (77%) in the control group. Both of these findings were not statistically significantly different between groups and the clinical significance was not discussed.

Summary

One study found that pharmacist prescribers were better at blood pressure management than doctors but the clinical significance of this was not discussed. In the remaining two studies, patient-mix adjustment was not made to account for differences in baseline characteristics and therefore no conclusion can be drawn from these studies.

Diabetes control

Two studies measured diabetes control to evaluate the effect of pharmacist prescribing on the outcomes of patient care.[23,24] Due to heterogeneity in study methodology (analytical method) and population, no meta-analysis was performed. Heterogeneity between studies was mainly due to differences in the race and gender of participants included in the two studies. The study population in Hawkins et al.[23] was mainly Mexican-American with over 75% being female while those in Jacobs et al.[24] were mainly Caucasian. A narrative description of the studies follows.

In both studies, the difference in means of post-test assessment between the two groups was used to measure the significance of the difference between arms. One study also calculated the significance of the change in mean HbA1c from baseline for both groups.[24] The remaining study did not present results for mean change in fasting BSL from baseline. Statistical significance could not be calculated as there were insufficient data presented in the paper.

Results for mean fasting BSL and HbA1c measured are summarized in Table 4.

In the study by Hawkins et al.,[23] the intervention group had a significantly higher baseline mean fasting BSL (p ≤ 0.05), which was adjusted using an analysis of covariance (ANCOVA). Analysis of covariance is a regression method which adjusts each patient's post-test measure for their baseline measure, with the advantage of being unaffected by baseline differences between groups.[36] This analysis showed no significant difference in mean fasting BSLs between arms post-trial (p = 0.058). The differences in baseline BSL between groups is likely to be due to the higher proportion of patients who were both hypertensive and diabetic in the intervention group, perhaps reflecting more advanced diabetes and therefore higher BSLs. Both arms had the same proportion of patients with diabetes without a diagnosis of hypertension.

Jacobs et al.[24] found that post-trial mean HbA1c was no different between arms at the end of six months, with mean HbA1c 8.1 +/− 1.2% in the intervention group and 8.2 +/− 1.2% in the control group (p = 0.597). However, at the end of 12 months, mean HbA1c was significantly lower in

Table 4: Diabetes control

Study details	Mean fasting blood sugar level (BSL)				Mean change from baseline	
	Intervention (mg/dL)		Control (mg/dL)		Intervention (mg/dL)	Control (mg/dL)
	Pre-trial	Post-trial	Pre-trial	Post-trial		
Hawkins *et al.*[23] RCT	192 +/− 46	184 +/− 42	182 +/− 39	189 +/− 49	−8	+7
	Pre-trial: p ≤ 0.05 Post-trial: p = 0.058					
Jacobs *et al.*[24] RCT	**Mean HbA1c**				**Mean change from baseline**	
	Intervention (%)		Control (%)		Intervention (%)	Control (%)
	Pre-trial	Post-trial	Pre-trial	Post-trial		
	9.5 +/− 1.1	7.7 +/− 1.3	9.2 +/− 1.0	8.4 +/− 1.6	−1.8	−0.8
	Pre-trial: p = 0.07 Post-trial: p = 0.003				p < 0.05	

HbA1c: glycosylated hemoglobin, RCT: randomized controlled trial.

the intervention arm (p = 0.003). Mean change in HbA1c from baseline to 12 months post-trial in both groups was also compared, with a reduction of 1.8% in the intervention group compared to an increase in 0.7% in the control group, a finding that was statistically significant (p <0.05). The clinical significance of these findings was not discussed.

One study also reported patient numbers achieving a predefined target HbA1c of equal or less than 7%.[24] At the end of 12 months, 19 patients (35%) in the intervention group achieved this target compared to 14 patients (21%) in the control group. This finding was not found to be statistically significant (p = 0.105).

Summary
Pharmacist prescribers manage blood sugar control in diabetics just as well as doctors. In one study pharmacist prescribers were statistically significantly better at managing blood sugar than doctors, although the clinical significance was not discussed.

Cholesterol control
Two studies measured cholesterol control to evaluate the effect of pharmacist prescribing on the outcomes of patient care.[24,27] In Jacobs *et al.*,[24] LDL cholesterol was the outcome measure while both LDL cholesterol and total cholesterol were measured by Weeks and Fyfe.[27] The results of these studies are presented in Table 5.

Meta-analysis was not performed for LDL cholesterol due to the small number of study participants in Weeks and Fyfe[27] (six in control, eight in intervention). Due to the significantly higher number of participants in Jacobs *et al.*[24] (92 in control, 72 in intervention), more weight would be assigned to this study, which would mask any study effects by Weeks and Fyfe.[27]

Mean LDL cholesterol in Jacobs *et al.*[24] was reported in mg/dL but was converted to mmol/L to allow comparison between studies. At the end of the trial, the intervention group was found to have a significantly lower LDL cholesterol compared to the control arm (p = 0.01) but the clinical significance of these results were not discussed.

Weeks and Fyfe[27] also reported an improvement in LDL cholesterol in both arms, with patients managed by the pharmacist prescriber lowering their LDL cholesterol by 1.3 mmol/L compared to 0.2 mmol/L in the doctor group. There was also a greater reduction in total cholesterol for patients in the intervention arm compared to the control arm (1.1 mmol/L versus 0.1 mmol/L). The results of this study could also indicate that repeated counselling and follow-up are important in helping patients to adhere to the treatment plan for cholesterol lowering. Due to the small sample size, no statistical analysis was performed in this study and caution should be used when interpreting the results.

Table 5: Low density lipoprotein cholesterol and total cholesterol

Mean LDL					Mean change from baseline	
Study details	Intervention (mmol/L)		Control (mmol/L)		Intervention (mmol/L)	Control (mmol/L)
	Pre-trial	Post-trial	Pre-trial	Post-trial		
Jacobs et al.[24] RCT	3.1 +/− 0.8	2.4 +/− 0.5	3.0 +/− 0.9	2.7 +/− 0.9	−0.7	−0.3
	Pre-trial: p = 0.227 Post-trial: p = 0.01					
Weeks and Fyfe[27] RCT	3.1	1.8	3.1	2.9	−1.3	−0.2
	No statistical analysis performed (sample size too small)					
Mean total cholesterol					Mean change from baseline	
Study details	Intervention (mmol/L)		Control (mmol/L)		Intervention (mmol/L)	Control (mmol/L)
	Pre-trial	Post-trial	Pre-trial	Post-trial		
Weeks and Fyfe[27] RCT	5.1	4.0	5.3	5.2	−1.1	−0.1
	No statistical analysis performed (sample size too small)					

LDL: low density lipoprotein, RCT: randomized controlled trial.

Jacobs et al.[24] also reported patient numbers achieving a predefined target LDL cholesterol of equal or less than 100 mg/dL (2.6 mmol/L). At the end of 12 months, 32 patients (62%) in the intervention group achieved this target compared to 24 patients (55%) in the control group. This finding was not found to be statistically significant (p = 0.537).

Summary
There is some evidence to suggest that pharmacist prescribers can manage cholesterol levels at least as well as doctors, with improvement in LDL cholesterol and total cholesterol. One study found patients of pharmacist prescribers had statistically significantly lower LDL post-trial than patients of doctors, but the clinical significance of this was not reported.

Overall summary – therapeutic failure or benefit
Pharmacist prescribers manage blood pressure, blood sugar and cholesterol levels just as well as doctors. In studies that reported measured endpoints, these were statistically significantly lower in the pharmacist prescriber group, although the clinical significance was not discussed.

Adverse events related to therapy
The six studies (two RCTs and four prospectively controlled quasi experimental studies) that reported adverse events as an outcome were all related to warfarin therapy and associated bleeding or thromboembolic events.[21,22,29,30,32,34] The classification of adverse events by severity occurred in some studies but not in others. Where classification of severity occurred, the definition of what constituted major or minor bleeding differed. All studies were underpowered to detect adverse effects related to therapy, mainly due to small effect size but also small sample sizes. Due to the heterogeneity of outcomes measured, no meta-analysis was performed. A narrative description of the studies follows and the results are presented in Table 6.

Chan et al.[21] reported the number of major bleeding events to be one (1.6 per 100 patient-years) in the intervention group and two (3.1 per 100 patient-years) in the control group, a finding that was not statistically significant (p = 1.0). No fatalities occurred due to bleeding in either group. The number of major thromboembolic events was one (1.6 per 100 patient-years) in both arms, a finding that was also not statistically significant (p = 1.0). No fatalities related to thromboembolic events occurred in either group.

Chenella et al.[22] found that four patients (10%) in the intervention arm suffered from minor bleeding events, compared to none in the control arm. No major bleeding events occurred in either arm. The significance of these findings was not reported. This study did not report thromboembolic events as a study outcome.

Table 6: Adverse events related to warfarin therapy

Study details	Number of bleeding events				Number of thromboembolic events		Number of deaths	
	Minor		Major					
	Int	Cont	Int	Cont	Int	Cont	Int	Cont
Chan et al.[21] RCT	Not reported		1 (1.6 ppy)	2 (3.1 ppy)	1 (1.6 ppy)	1 (1.6 ppy)	0	0
			p = 1.00		p = 1.00			
Chenella et al.[22] RCT	4 (10%)	0	0	0	Not reported		0	0
	Significance not reported							
Burns[29] Quasi experimental	Combined bleeding/thromboembolic events: Int: 6% (2 strokes) Cont: 12% (1 stroke and 3 bleeding events) Significance not reported						0	1
Damaske and Baird[30] Quasi experimental	2 (7%)	3 (14%)	0	0	0	0	0	0
	Significance not reported							
Schillig et al.[32] Quasi experimental	Not reported		2 (0.8%)	1 (0.4%)	0	0	0	0
			p = 0.563					
Chau et al.[34] Quasi experimental	1 (3%)	2 (6%)	0	2 (6%)	0	1 (2%)	0	1 (2%)
	Significance not reported							

Cont: control, Int: intervention, ppy: per 100 patient-years, RCT: randomized controlled trial.

Burns[29] reported the combined total of adverse events, which equated to 6% (two strokes) in the intervention arm and 12% (one stroke and three bleeding events) in the comparator arm. The significance of this finding was not reported.

Chau et al.[34] reported the number of bleeding events (minor and major), the number of venous thromboembolisms and number of deaths that occurred in each arm. Minor bleeding events occurred in one (3%) and two (6%) patients in the intervention and comparator arm bleeding respectively. There were no occurrences of major bleeding events in the intervention arm compared to two (6%) in the comparator arm. No life-threatening bleeding events occurred in either arm. No pulmonary embolisms or deaths were reported in the intervention arm while one patient (2%) in the comparator arm developed a pulmonary embolism which resulted in death. Deep vein thrombosis was not reported in either arm. Both statistical and clinical significance of the findings was not reported.

Damaske and Baird[30] reported that two (7%) bleeding events occurred in the intervention arm and three (14%) in the comparator arm. All events were considered minor by the attending doctors. The statistical and clinical significance of this finding was not reported. No other adverse events occurred in either arm.

In Schillig et al.,[32] two (0.8%) major bleeding events occurred in the intervention arm compared to one (0.4%) in the comparator arm. This finding was not statistically significant (p = 0.563). No thromboembolic events occurred in either group.

Summary
For all studies, outcome data for bleeding or thromboembolic events were small. Bleeding events were classified by severity except in the case of Burns[29] where combined bleeding and thromboembolic events were reported. Where statistical analysis was performed, no significant differences were found between the control and intervention groups.[21,32] In the remaining four studies which did not perform statistical analysis, the outcomes measured were not dissimilar, but interpretation of the results is difficult due to the small number of events.[22,29,30,34] In all cases, the studies were underpowered to detect a difference in incidence of adverse effects between the intervention and control groups and therefore a meaningful conclusion cannot be drawn.

Appropriateness of prescriptions and prescribing errors
A number of studies reported appropriateness of medication orders prescribed, prescribing errors

and medications omitted from the medication chart. This is discussed in further detail below, with a summary of the results presented in Table 7.

Appropriateness of medication orders prescribed

One RCT and two quasi experimental studies reported appropriateness of prescribing as an outcome measure.[19,29,30] Due to heterogeneity in study methodology, population and the outcome measured, no meta-analysis was performed. A narrative description of the studies follows.

In the RCT by Hale et al.,[19] appropriateness of venous thromboembolism (VTE) prophylaxis (chemical or mechanical) was assessed in tandem by two assessors and rated in accordance with local and national guidelines. There was a statistically significant difference (p < 0.001) between percentages of appropriate VTE prophylaxis prescriptions in the intervention arm (93.8%) compared to the control arm (63.9%) in the preadmission clinic. There was no statistical difference between arms when the prescriptions were assessed for patients on admission with 93.1% prescriptions deemed appropriate in the intervention arm compared to 89.5% in the control arm.

Burns[29] found that for patients who required a loading dose with warfarin, all 14 patients (100%) were dosed appropriately in the intervention group compared to 11 (73%) in the comparator group. The statistical significance of these findings was not reported by the authors, but a Fisher's exact test showed no statistically significant difference between groups (p = 0.1). Following a loading dose with warfarin, the number of patients who received an appropriate maintenance dose was 14 (100%) in the intervention group and seven (46%) in the comparator group, a finding that was statistically significant (p < 0.001)

In Damaske and Baird,[30] all 29 patients (100%) in the intervention arm were dosed appropriately with warfarin compared to 15 patients (68%) in the comparator arm. The significance of these findings was not reported by the authors but a Fisher's exact test showed no statistically significant difference between groups (p = 0.21).

Summary

There was no difference in the appropriateness of warfarin prescribing between pharmacists and doctors except in the prescribing of maintenance doses in one study where pharmacists were found to be more compliant with existing guidelines. In the prescription of VTE prophylaxis, pharmacists were found to be better at following recommended guidelines than doctors when the medication charts were assessed in a preadmission clinic. However, there were no differences between prescribing arms when the medication charts were assessed on patients' hospital admission.

Prescriptions requiring modification by a doctor

Three RCTs reported on prescriptions which required modification by a doctor subsequent to pharmacist prescribing, by either comparing prescribing between arms or by auditing management plans made by the pharmacist.[19,20,22,23] Meta-analysis was not possible so a narrative description of the studies follows.

Table 7: Appropriateness of prescribing

Study details	Medications prescribed	Prescribing assessed	Results		
			Intervention	Control	P value
Hale et al.[19] RCT	Thromboembolism prophylaxis (chemical or mechanical)	Appropriately prescribed in preadmission clinic	93.8%	63.9%	p < 0.001
		Appropriately prescribed on admission	93.1%	89.5%	p = 0.29
Burns[29] Quasi experimental	Warfarin	Appropriately prescribed loading doses (% patients)	100% (n = 14/14)	73% (n = 11/15)	Significance not reported Fisher's exact test: p = 0.1
		Appropriately prescribed maintenance doses (% patients)	100% (n = 14/14)	46% (n = 7/15)	F (1, 26) = 17.33, p < 0.001
Damaske and Baird[30] Quasi experimental	Warfarin	Appropriately prescribed first dose of 5 mg (% patients)	100% (n = 29/29)	68% (n = 15/22)	Significance not reported Fisher's exact test: p = 0.21

RCT: randomized controlled trial.

Hale et al.[20] reported that of the 194 patients prescribed medications by the pharmacist in the intervention arm, 10 charts were amended by a doctor. Of this number, five were considered minor changes and three were the addition of analgesics which were out of the pharmacist's prescribing scope. The remaining two changes were related to VTE prophylaxis, of which a change by the doctor resulted in inappropriate VTE prophylaxis according to local and national guidelines.

In Chenella et al.,[22] patients were prescribed anticoagulants (heparin and warfarin) by the doctor group or the pharmacist-prescriber group. With each prescription, the clinician in the other arm simulated prescribing in a blinded fashion on a data collection sheet. The simulated dose was not disclosed to the clinician in the other arm, or administered to the patients. Regression lines were used to compare actual and simulated doses for patients in both groups and were found to be closely correlated for both heparin and warfarin in each arm.

In Hawkins et al.,[23] all patient-care assessments and plans made by the pharmacist were subsequently reviewed by doctor auditors to assure the provision of adequate medical care to patients. A prospective evaluation of doctor acceptance of the pharmacist's plans during the first 18 months of the study showed that 99% of these plans were accepted without modification.

Summary
Where doctors independently assessed pharmacist prescribing, they were mainly in agreeance with therapeutic plans made and doses prescribed by pharmacists.

Prescribing errors
Two RCTs and one quasi experimental study included in this review included prescribing errors as an outcome measure.[19,20,25,33] In all three studies, the prescribing errors reported were clinical errors (e.g. errors in prescription of a medication, dose, frequency or route) which can potentially lead to errors in administering medication to the patient, resulting in clinically significant adverse events. This is distinguished from documentation errors (e.g. unsigned prescription, date of prescription omitted) which does not usually lead to an error of clinical significance. A meta-analysis of clinical errors reported in three studies was not possible as one RCT provided insufficient data to allow this.[25] These results are summarized in Table 8.

A narrative description of the studies follows.

Hale et al.[19] defined prescribing errors as those related to medication, dose or frequency, and communication errors as prescriptions that were rated as ambiguous or unclear. The study found significantly less prescribing errors ($p < 0.001$) in the intervention group (0.2% of orders) compared to the control group (6.3% of orders).

A sub-analysis of 5% of trial participants (randomized sample) in Hale et al.[19] was reported in Hale et al.[20] A panel, blinded to patient allocation, was convened to assess the appropriateness of prescriptions and a modified Medication Appropriateness Index was used to assess the appropriateness of prescribing.[37] Based on the overall combined assessment of all panel members, the number of prescriptions deemed inappropriate was 13 from 266 prescriptions (4.9%) in the intervention arm and 32 from 294 prescriptions (10.9%) in the control arm. The significance of this finding was not reported but analysis using Fisher's exact test shows a statistically significant difference between groups ($p = 0.01$). Based on individual reviewers' assessments, the difference in groups was only statistically significant when assessed by the pharmacist, with six of 61 medications assessed as inappropriate in the control arm compared to zero of 64 in the intervention arm ($p = 0.029$). Assessments by the remainder of the panel which consisted of an anesthetist, pharmacologist, nurse, resident medical officer (RMO) and surgeon did not find any statistically significant difference in the number of inappropriate medications between arms. The total number of medications reviewed by each individual assessor and total number of medications rated as inappropriate by each assessor (apart from that of the pharmacist) were reported as a combined number for the intervention and control group, and therefore further comparison between arms was not possible.

Marotti et al.[25] reported on incorrect doses and incorrect frequencies of medications charted. Outcome measures were collected by an independent technician. The average number of incorrect doses was found to be 0.02 and 0.48 in the intervention and control groups, respectively ($p < 0.05$). The average number of incorrect medication frequencies charted was 0.015 and 0.29 in the intervention and control groups, respectively ($p < 0.05$).

Table 8: Prescribing errors

Study details	Errors assessed		Results		
			Intervention	Control	P value
Hale *et al.*[19] RCT	Incorrect medication, dose or frequency (total number)		2 (0.2%)	51 (6.3%)	p < 0.001
	Communication errors (total number ambiguous or unclear prescriptions)		208/904 (23%)	445/1034 (43%)	p < 0.001
Marotti *et al.*[25] RCT	Incorrect doses charted (average number)		0.02 (CI 0–0.04)	0.48 (CI 0.35–0.61)	p < 0.05
	Incorrect frequencies charted (average number)		0.015 (95% CI 0–0.06)	0.29 (95% CI 0.19–0.39)	p < 0.05
Tong *et al.*[33] Quasi experimental	Total patients with errors		15 (3.7%)	372 (78.7%)	p < 0.001
	[Errors per patient (total number)	Zero errors	393 (96.3%)	101 (21.3%)	p < 0.001
		One to two errors	15 (3.7%)	145 (30.6%)	
		Three to four errors	0	101 (21.3%)	
	Severity of error per patient (total number)	Severity rating 1 or 2 (Insignificant to low risk)	10 (2.4%)	116 (24.5%)	p = 0.01
		Severity rating 3 or 4 (Moderate to high risk)	5 (1.2%)	231 (48.8%)	
		Severity rating 5 (Extreme risk)	0	25 (5.3%)	
	Errors by type (total number)	Omitted medication	12	1397	p < 0.01
		Incorrect dose	7	138	
		Incorrect frequency	0	5	
		Incorrect/unnecessary medication	0	33	
		Incorrect route	0	0	

CI: confidence interval, RCT: randomized controlled trial.

Tong *et al.*[33] defined medication errors as prescriptions with an omitted medication, incorrect dose or frequency, incorrect or unnecessary medication or incorrect medication route), which were detected within 24 hours of admission. Errors were identified by an independent pharmacist assessor who was not blinded to randomization. These errors were then reviewed and assigned a risk rating by a blinded independent expert panel comprising a general doctor, an emergency doctor and a senior clinical pharmacist. The study found that the number of patients with medication errors were 15 (3.7%) in the intervention arm and 372 (78.8%) in the comparator arm, a finding that was statistically significant (p < 0.001). The number of errors detected per patient was also significantly lower in the intervention arm (p < 0.001) – pharmacist prescribers made no errors in 393 patients (96.3%) and did not make more than two errors per patient. In the comparator arm, doctors made no errors in 101 patients (21.3%) and five errors or more in 126 patients (26.6%). Errors were then classified as insignificant, low risk, moderate risk, high risk or extreme risk (catastrophic), defined as follows:[38[p.S45]]

- "Insignificant: No harm or injuries; low financial loss
- Low: Minor injuries, minor treatment required, no increased length of stay or readmission, minor financial loss
- Moderate: Major temporary injury, increased length of stay or re-admission, cancellation or

delay in planned treatment or procedure. Potential for financial loss

- High: Major permanent injury, increased length of stay or readmission, morbidity at discharge, potential for significant financial loss
- Catastrophic: Death, large financial loss and/or threat to goodwill/good name"

Pharmacists made significantly less errors in all categories (p = 0.01), with four errors (1%) classed as moderate risk, one error (0.2%) as high risk and no errors that conferred extreme risk to the patient. In contrast, doctors were found to have made 81 errors (17.1%) of moderate risk, 150 errors (31.7%) of high risk and 25 errors (5.3%) of extreme risk. The most frequently made error in both groups was for medicines omitted from the medication chart. The authors reported on a "number to treat" analysis, which found one case of high risk or extreme error was prevented for every three patients reviewed and prescribed medications by the pharmacist.

Summary

All three studies found that pharmacist prescribers made significantly less clinical prescribing errors than doctors. In two studies, the results were unlikely to be influenced by assessor bias as the outcome assessors were blinded to patient allocation. In a subanalysis of one study, no difference was found in
inappropriateness of prescriptions between arms. One study found that pharmacist prescribers had less patients with medication errors, fewer errors per patients and less errors that conferred a moderate, high or extreme risk to the patient.

Medication omissions

Four papers (related to three studies) included in this review also reported on medication omissions separately to prescribing errors as an outcome measure. Due to the different study methodologies (two RCTs,[19,20,25] one quasi experimental trial),[33] the results were not combined in a meta-analysis. A narrative description of the studies follows, with the results summarized in Table 9.

In Hale et al.,[19] the total number of medications omitted from the prescription chart in the intervention group was 11 (1.2%), of which three (0.3%) were regular medications and eight (0.9%) were *pro re nata* (when required) medications. In the control group, there were a total of 383 medications (31.5%) omitted from the prescription chart, of which 248 (20.4%) were regular medications and 135 (11.1%) *pro re nata* medications. The difference between arms for regular medications was statistically significant (p < 0.001). The odds ratio for an order in the control group to be omitted, compared to the intervention group, was 41 (95% CI, 20.6,

Table 9: Medication omissions

Study details	Medication omissions (not prescribed) (Total number)	Results		
		Intervention	Control	P value
Hale et al.[19] RCT	Regular medications	3/887 (0.3%)	248/1217 (20.4%)	p < 0.001
	"When required" medications	8/887 (0.9%)	135/1217 (11.1%)	*Significance not reported* Fisher's exact test: p < 0.0001
Hale et al.[20] RCT	Regular medications	1/55 (2%)	25/89 (28%)	p < 0.001
Marotti et al.[25] RCT	Not specified as regular or "when required" medications (Mean number)	1.07 (95% CI 0.9–1.25)	3.21 (95% CI 2.89–3.52)	p = 0.002
Tong et al.[33] Quasi experimental	Not specified as regular or "when required" medications	12	1397	p < 0.01

CI: confidence interval, RCT: randomized controlled trial.

81.8; p < 0.001). This analysis was adjusted for the total number of medications patients were taking, which was higher in the control group than in the intervention group (1364 versus 983). Results were not adjusted for patient mix. A greater number of total medications in the control arm biased the study to pharmacist prescribing and while adjustments were made, residual confounding may still be present. The statistical significance of the difference between arms for *pro re nata* medications was not reported, but p value was calculated to be less than 0.0001 using Fisher's exact test.

In a subset analysis of 5% of the patient population in the study by Hale et al.,[20] the number of regular medications omitted from the chart was found to be one out of 55 (2%) for the intervention group and 25 out of 89 (28%) in the control group which was statistically significant (p < 0.001). The clinical significance of medication omissions was assessed by an independent panel; only one of six reviewers thought the single occurrence of omission was significant. In the control group, the average across the panel showed just under half of omissions had the potential to cause patient harm.

Marotti et al.[25] found that the mean number of medication omissions was 1.07 in the intervention group and 3.21 in the control group, a finding that was statistically significantly different (p = 0.002).

In Tong et al.,[33] the number of medication omissions was 12 in the intervention group and 1397 in the comparator group, a finding which was statistically significant (p < 0.01).

Summary
In three studies, the pharmacist prescriber group made less medication omissions compared to the doctor group. In one study, nearly half of the medication omissions in the control group were judged to have the potential to cause patient harm.

Overall summary – appropriateness of prescriptions and prescribing errors
The evidence shows pharmacists prescribed warfarin doses just as well as doctors; there is some evidence to suggest that pharmacists adhere to dosing guidelines better than doctors.

When studied, pharmacists make significantly less clinical prescribing errors than doctors, in addition to having fewer errors that confer a moderate, high, or extreme risk to the patient.

Doctors were mainly in agreeance with therapeutic plans made and doses prescribed by pharmacists.

Pharmacist prescribing resulted in significantly less medication omissions compared to doctor prescribing; nearly half of medication omissions by doctors were rated to have the potential to cause patient harm compared to none in the pharmacist prescribing arm.

Anticoagulant prescribing – International Normalized Ratio (INR) control and time to therapeutic range
INR in therapeutic range
Of the seven studies on warfarin prescribing, one RCT and three quasi experimental studies reported INR in therapeutic range as an outcome measure.[21,28,29,34] However, these studies varied in their measurements of the outcome, either at the time of measure (e.g. Day 4 versus at discharge) or by unit of measure (e.g. patient-time within range versus percentage patients or INR within range). Due to heterogeneity in populations and the outcome measured, no meta-analysis was performed. A narrative description of the studies follows.

Chan et al.[21] reported that patient-time spent within target INR range was 64% for the intervention group and 59% for the control group, a statistically significant difference (p < 0.001). Patient-time in extended target range (defined as +/− 0.2 INR units) was 78% and 76% for the intervention and control arm respectively, a finding that was also statistically significant (p < 0.001).

In Boddy,[28] the percentage of INRs within target range from Day 4 onwards was 58% in the intervention group and 18% in the control group, which was statistically significant (p < 0.001).

Burns[29] found that for patients who required loading with warfarin, the percentage who were within target range on Day 4 after loading was 57% for the intervention group and 46% for the comparator group (p = 0.72). On discharge or transfer to another ward, 68% of patients in the intervention arm were within target range compared to 73% in the comparator arm (p = 0.77). At the outpatient clinic, 61% of patents in the intervention group were within target range compared to 79% in the comparator arm (p = 0.32). The statistical significance of these findings was not reported by the authors; p values reported above were calculated using the Fisher's exact test.

Chau et al.[34] reported that the proportion of INRs within target range was 67.9% in the intervention arm and 50.9% in the comparator arm. The statistical significance of this was not reported; the Fisher's exact test could not be used to calculate the p value as the total number of INR tests performed was not reported.

Summary

The four studies described above were conducted in different hospital settings (one outpatient clinic and three inpatient wards) with adult patients of varying ages (one study in elderly patients and one excluding elderly patients). In one study, all study participants were Chinese. Patients were admitted under medical units or rehabilitation units (following orthopedic intervention or stroke). In one study,[34] doctors did not have access to a warfarin dosing nomogram while the pharmacist prescribers did. In the remaining three studies, both arms used a warfarin dosing nomogram.

Two studies show a statistically significant improvement in INR in therapeutic range in the pharmacist prescriber group compared to usual care by medical staff.[21,28] Another study showed improvement in the intervention arm but the statistical significance was not reported.[34] The remaining study did not show any statistically significant differences between arms at any stage of the patient journey.[29] These results indicate that pharmacist prescribers are able to maintain INR in therapeutic range just as well as doctors. These results are summarized in Table 10.

Subtherapeutic or Supratherapeutic INR

Five controlled quasi experimental trials reported INR above or below therapeutic range as an outcome measure.[28-30,32,34] However, these studies varied in their measurements of INRs above the therapeutic range (e.g. patients with an INR > 3.0 versus > 5.0 versus > 6.0). The studies also varied in the reported unit of measure (e.g. percentage INRs versus percentage patients). Due to heterogeneity in populations and the outcome measured, no meta-analysis was performed. A narrative description of the studies follows.

In Boddy,[28] INRs below 2.0 and above 6.0 from Day 4 onwards were outcome measures of interest. In most clinical scenarios, an INR below 2.0 is considered subtherapeutic and puts the patient at

risk of thromboembolic events. In all cases, an INR above 6.0 is considered supratherapeutic and increases a patient's risk of bleeding. The percentage of INRs below 2.0 was 10% in the intervention arm and 32% in the comparator arm while the percentage of INRs above 6.0 was 1% in the intervention arm and 5% in the comparator arm. Statistical significance was not reported and there was no discussion of the clinical significance of these results.

Burns[29] reported on the percentage of patients who had a subtherapeutic or supratherapeutic INR (+/− 0.2 INR units) at some point during their stay. In the intervention arm, 67% patients were either under- or over-anticoagulated compared to 91% patients in the comparator arm, a finding that was statistically significant (p = 0.016).

In Chau et al.,[34] the percentage of subtherapeutic INRs (INR < 2.0) was 22.7% in the intervention arm and 33.2% in the comparator arm. The percentage of supratherapeutic INRs (INR > 3.0) was 9.4% in the intervention arm and 14.9% in the control arm. No patients had an INR above 6.0 in either arm.

Damaske and Baird[30] did not collect data on patients with subtherapeutic INRs. The percentage of patients with supratherapeutic INRs (any value above target range) was reported to be 17% for the intervention group (INR range 3.3 – 7.4 for five patients) and 27% for the comparator group (INR range 3.4 – 6.2 for six patients). The statistical significance of this result was not reported.

In Schillig et al.,[32] the percentage of INRs above 5.0 was reported to be 9.6% in the intervention group and 14.8% in the comparator group, a finding that was not statistically significant (p = 0.076).

Summary

The five studies described above were all conducted in the inpatient setting with patients admitted under different treating units, including medical, respiratory, rehabilitation (following orthopedic intervention or stroke), cardiology and vascular units. In two studies,[28,29] clinicians used a warfarin nomogram while only pharmacist prescribers had access to the nomogram in another.[34] For the two remaining studies, it is unclear whether medical staff had access to a nomogram in one,[30] and in the other it is not specified whether a nomogram was used.[32]

Table 10: International normalized ratio (INR) control

Study details	INR measurement	Unit and time of measure	Results		
			Intervention	Control	P value
Chan et al.[21] RCT	In therapeutic range	Patient time	64%	59%	p < 0.001
		Patient time in extended target INR range (+/− 0.2 INR units)	78%	76%	p < 0.001
Boddy[28] Quasi experimental	In therapeutic range	Percentage INRs from Day 4 onwards	58%	18%	p < 0.001
	Sub-therapeutic	Percentage INRs < 2.0 from Day 4 onwards	10%	32%	Not reported
	Supra-therapeutic	Percentage INRs > 6.0 from Day 4 onwards	1%	5%	
Burns[29] Quasi experimental	In therapeutic range	Percentage patients on Day 4 after loading	57% (8/14)	46% (7/15)	Not reported Fisher's exact test: p = 0.72
		Percentage patients on discharge or transfer to another ward	68% (19/28)	73% (22/30)	Not reported Fisher's exact test: p = 0.77
		Percentage patients at the Outpatient clinic	61% (13/21)	79% (19/24)	Not reported Fisher's exact test: p = 0.32
	Sub- or supra-therapeutic	Percentage patients (+/− 0.2 INR units)	67% (22/33)	91% (30/33)	F (1, 64) = 6.17, p = 0.016
Damaske and Baird[30] Quasi experimental	Supra-therapeutic	Percentage patients	17%	27%	Not reported
Schillig et al.[32] Quasi experimental	Supra-therapeutic	Percentage INRs > 5.0	9.6%	14.8%	p = 0.076
Chau et al.[34] Quasi experimental	In therapeutic range	Percentage INRs	67.9%	50.9%	Not reported
	Sub-therapeutic	Percentage INRs < 2.0	22.7%	33.2%	
	Supra-therapeutic	Percentage INRs 3.01 −3.99	9.1%	12.8%	
		Percentage INRs 4.0 − 6.0	0.3%	2.1%	
		Percentage INRs > 6.0	0%	0%	

RCT, randomized controlled trial

In all five studies, the intervention arm performed better than the comparator arm but the statistical significance was not reported in three studies.[28,30,34] In the remaining two studies, one showed statistical difference favoring the intervention arm,[29] while the other did not show any statistical difference between groups.[32] While none of these studies discuss the clinical significance of the findings, they indicate that pharmacists who prescribe warfarin according to a nomogram are able to maintain INR in therapeutic range just as well as doctors.

Time to therapeutic range

Four studies on anticoagulant prescribing reported time taken to achieve therapeutic range as an outcome measure. Of the four studies, one was related to warfarin and heparin,[22] two to warfarin,[30,34] and the other to heparin.[31] One study was a RCT,[22] while the remaining three were quasi experimental studies.[30,31,34] Due to the different anticoagulants studied and the heterogeneity of outcomes measured, no meta-analysis was performed. A narrative description of the studies follows.

In Chenella et al.,[22] the mean number of days taken to achieve therapeutic proconvertin and prothrombin in inpatients who required continuous intravenous heparin and oral warfarin was $5.7 +/- 1.4$ in the intervention group and $5.8 +/- 2.1$ in the control group, the difference of which was not statistically significant.

In Chau et al.,[34] the mean time taken from commencement of warfarin therapy to first therapeutic INR was 2.8 days (range 0 – 10) in the intervention group and 3.0 days (range 0 – 14) in the comparator group. The significance of this finding was not reported but the difference in time reported to achieve target INR is not considered clinically relevant.

Damaske and Baird[30] reported the average time taken to achieve therapeutic INR from commencement of warfarin therapy. The average time taken was 6.0 days (range 4 – 11) in the intervention group and 5.6 days (range 4 – 11) in the comparator group. The statistical significance of this finding was not reported but the difference in time reported to achieve target INR is not considered clinically relevant.

For the two phases reported in the study by Pawloski and Kersh,[31] in Phase I, the mean time (hours) to therapeutic APTT (activated partial thromboplastin time) was $16.52 +/- 10.92$ in the intervention arm and $46.5 +/- 34.13$ in the comparator arm, while in Phase II, this was reported to be $9.32 +/- 3.78$ in the intervention arm and $31.64 +/- 32.74$ in the comparator arm. In both phases, the difference in control and intervention arms was found to be statistically significant ($p < 0.001$). In both phases, there was no statistically significant difference in the mean number of days of heparin therapy per patient.

Summary

The four studies report varied results, with one finding that pharmacist prescribers achieved therapeutic range sooner when compared to doctors,[31] another showing no difference between arms,[22] and the remaining two studies not reporting statistical significance but reporting similar results across arms.[30,34] These results indicate that when prescribing anticoagulants according to a dosing nomogram, pharmacists achieve therapeutic range around the same time as doctors. The clinical significance of the findings was not discussed in these studies but the results suggest no clinical difference.

Overall summary – INR control

Pharmacists who prescribe warfarin according to a nomogram achieve therapeutic range within the same time period as doctors and maintain INR in therapeutic range just as well as doctors.

Patient satisfaction

Two RCTs included in the review reported patient satisfaction as an outcome measure.[21,26] Due to heterogeneity in populations and the outcome measured, no meta-analysis was performed. The results are summarized in Table 11 and a narrative description of the studies follows.

In the study by Chan et al.,[21] patients recruited in each arm were administered the patient satisfaction questionnaire (PSQ)-18 (RAND Corporation, USA) in an interview by a research assistant who was not blinded to patient allocation. When rating their general satisfaction, the intervention group scored a $3.8 +/- 0.5$ and the control group scored a $4.0 +/- 0.5$, which was not statistically significantly different ($p = 0.134$). Statistically significant differences between arms in favor of the pharmacist prescribing arm was found in terms of the amount of time spent with the clinician ($p < 0.001$) and accessibility of the clinician ($p < 0.001$). There were no statistically significant differences between arms in terms of technical quality, interpersonal manner, communication and financial costs.

In Vivian,[26] patients were administered a patient satisfaction survey at baseline and at the end of the study. Patients were asked to respond to a variety of statements with either "most of the time", "sometimes", "very rarely", or "never". Patients responded to the statement "I am very satisfied with the pharmacy services that I receive" with "most of the time" in 88% patients in the intervention group compared to 68% patients in the control group who only received traditional pharmacy services (medication dispensing and counselling). This finding was not statistically significant ($p = 0.098$). No significant changes were noted in either group from baseline to end of study. There was no statistically significant difference between arms for all other parameters measured except in the case of distractions in the clinic area which led to poor service. In this case, less distractions leading to poor service were found in the pharmacist prescribing arm ($p < 0.018$).

Table 11: Patient satisfaction survey

Study details	Survey details	Assessment
Chan et al.[21] RCT	Patient satisfaction questionnaire (PSQ)-18 (RAND Corporation, USA), administered by a research assistant not blinded to patient allocation	*General satisfaction* Intervention: $3.8 +/- 0.5$, $p = 0.134$ Control: $4.0 +/- 0.5$ *Overall mean score* (includes scores for technical quality, interpersonal manner, communication, financial aspect, time spent, accessibility) Intervention: $3.8 +/- 0.2$ Control: $3.6 +/- 0.3$ $p < 0.001$
Vivian[26] RCT	Patient satisfaction survey at the end of study	*Patients who responded to statement: "I am very satisfied with the pharmacy services that I receive" with "most of the time"* (Data for sometimes, very rarely and never not reported in the study) Intervention: 88% Control: 68% $p = 0.098$

RCT: randomized controlled trial.

Summary

In two studies that reported on patient satisfaction, patients were found to be as satisfied with the care provided by pharmacist prescribers as with doctors.

Discussion

Non-medical prescribing is well described in the literature, particularly in the field of nursing. However, published information on pharmacist prescribing is mainly limited to descriptions of the practice, barriers to implementation or perceptions of relevant stakeholders on pharmacist prescribing. Some systematic reviews have evaluated the impact of pharmacist prescribing, but included data from both the community and hospital setting, or presented results for combined data with other non-medical prescribers.[3,10,11] A systematic review on the effects of pharmacist prescribing on patient outcomes in the hospital has not been previously undertaken and it is important that health policy-makers are informed about the safety and effectiveness of this intervention in easing the burden on the healthcare system.

This review identified studies which assessed prescribing by protocol,[21,22,26,28-31,34] supplementary prescribing,[19,24,25,33] and collaborative prescribing.[23,27]

In the majority of studies, pharmacists used dosing nomograms to prescribe heparin or warfarin. Prescribing by protocol is the least independent form of prescribing, where the pharmacist is required to prescribe initial and subsequent doses of medication based on a pre-existing guideline or dosing nomogram. This form of prescribing is non-complicated, and most pharmacists should be able to perform this task within their scope of practice, which may explain the large number of studies using this model of prescribing.[21,22,28-32,34] It is also a natural extension of a pharmacist's duty, which may make it more acceptable to doctors and hence easier to implement in a hospital setting.

In studies trialing the supplementary prescribing model, pharmacists were not limited to the prescription of a particular type of medication.[19,20,24,25,33] The studies were conducted among patients being admitted for elective surgery (i.e. in the preadmission clinic), in the ambulatory setting and in the inpatient setting. Three studies on supplementary prescribing were conducted in Australia and one in the USA, which likely reflects increasing interest of Australian pharmacist practitioners in expanding their scope of practice, given that pharmacist prescribing has not been legalized in Australia.

Collaborative prescribing is the most autonomous model of prescribing, and well suited for the outpatient setting as there is invariably less interaction required between the doctor and pharmacist. The high level of autonomy required for collaborative prescribing means that pharmacist prescribers need to be specialized or trained in their area of practice, which also explains the small number of studies using this model of prescribing.[23,27]

Regardless of the prescribing model used, all studies demonstrated that pharmacist prescribing is at least as safe as doctor prescribing. The strongest evidence was for supplementary prescribing of patients' medications on admission to hospital where the quality was moderate. Two of the three included studies were RCTs;[24,25] two trials had an independent panel who were blinded to participant allocation reviewing prescription errors using a medication appropriateness index.[20,33] The medication appropriateness index standardizes the assessment of the quality of prescribing by making it less subjective and therefore more reliable.

A number of clinically significant outcomes were found in terms of prescribing errors. Pharmacist prescribers were found to be 21 and 31 times less likely than doctors to make prescribing errors in two studies, respectively.[19,33] Pharmacists were also found to make less errors per patient, and errors were identified in a smaller number of patients.[33] In the same study, the proportion of patients with an error severity rating of moderate to high was 1.2% in the intervention group and 48.8% in the control group; no patients in the intervention group were assigned an extreme risk rating compared to 5.3% of patients in the control group. The difference in the number of patients assigned a moderate, high or extreme risk is of major clinical significance. Collectively, these severity categories of moderate, high or extreme are associated with increased length of stay or readmission, morbidity at discharge, or death of the patient. In addition to the negative health impact on the patient, moderate, high or extreme errors are associated with an increased burden on the healthcare system financially.

Prescribing errors are well documented in the literature and can be attributed to many factors including human error, lack of clinician knowledge or experience and system failure.[39-41] In many countries, hospital-based prescribing is carried out mainly by junior doctors. Their training in diagnosis and multiple modalities of treatment and limited clinical experience mean that they have had less exposure to medications in practice, and may have little knowledge of usual recommended doses, drug interactions and adverse drug reactions, which can lead to an increased incidence of prescribing errors.[42]

Pharmacists are trained in therapeutics and drug management for patients. By nature of the profession, they are exposed to a greater range of medications and have a broad knowledge of them. It is therefore not unexpected that pharmacists make less prescribing errors than doctors, especially when compared to junior doctors. The idea of pharmacists being part of a clinical team and acting as a defense against prescribing errors is not new. Studies have shown the benefits of pharmacist interventions in the hospital setting;[43] if these benefits can also be shown with pharmacist prescribing, then the expansion of pharmacy services to include this service can be justified.

The evidence in this review showed pharmacists were also found to have a statistically significantly lower rate of medication omissions compared to doctors; a finding also considered clinically significant.[19,33] Hospital pharmacists have been described as more likely to exhibit behaviors in line with conscientiousness.[44,45] People with this trait are usually more able to follow norms and rules (i.e. be more process driven) and have the ability to complete a task correctly. This, combined with their broader knowledge of medicines, may explain why pharmacists have been found less likely to omit patients' medications on admission compared to doctors.

All other outcome measures examined in this review were assessed to have a low quality of evidence. This included therapeutic failure or benefit (cardiovascular disease), adverse effects related to anticoagulant therapy, appropriateness of warfarin doses prescribed and effectiveness of anticoagulation prescribing.

The evidence for cardiovascular benefit due to pharmacist prescribing was derived from RCTs but the level of evidence was downgraded mainly due to poor methodology (lack of allocation concealment or blinding) and small sample size. All studies used surrogate endpoints (biomarkers) as the measure of effectiveness of therapy. Generally, biomarkers are used for a number of reasons. They are cheaper and easier to measure than the outcome of interest (e.g. blood pressure measurement versus morbidity and mortality from hypertension) and can be measured more quickly and earlier (e.g. cholesterol levels

measured with a blood test versus collecting mortality data over several years).[46]

The GRADE Handbook recommends that when surrogate endpoints are used, the level of evidence should be downgraded for indirectness.[18] However, contrary to this recommendation, the level of evidence was not downgraded for the use of blood pressure, blood sugar control and cholesterol as surrogate endpoints for cardiovascular morbidity and mortality. There is good evidence to show that lowering of these biomarkers is associated with cardiovascular benefits, i.e. blood pressure reduction with antihypertensive medication(s) is associated with cardiovascular protection,[47-49] blood sugar control reduces incidence and progression of microvascular complications (retinopathy, nephropathy, neuropathy) in both type I and type 2 diabetics,[50,51] diabetic patients with hypertension have less microvascular and macrovascular complications when target blood pressure is less than 150/85 mmHg,[52,53] intensive blood sugar control significantly reduces coronary events,[54-56] and for every reduction of 1 mmol/L in LDL, there is a corresponding 22% reduction in cardiovascular morbidity and mortality.[57] Studies have also shown that lowering LDL with statin therapy in patients with type 2 diabetes leads to fewer cardiovascular events.[58,59]

For the outcome of blood pressure management, a meaningful conclusion could only be drawn from one study due to failure to adjust for baseline differences in the remaining studies. Hawkins et al.[23] reported that pharmacists can manage blood pressure as well as doctors. There was no clinically significant differences between arms for blood pressure management in this study.

For the outcome of diabetes control, the two studies that assessed this found a mean reduction in post-trial BSL or HbA1c in the intervention arm, a finding that was clinically significant as any improvement in blood sugar control is correlated with a reduction in microvascular disease associated with diabetes.[53] In one study, 35% of patients in the intervention group compared to 21% patients in the control group achieved HbA1c of 7% or less.[24] An adequately powered study in this area should be a priority for future research because if found to be statistically significant the effect size suggested by this study would be clinically significant as it equates to one extra patient achieving target HbA1c in the intervention group for every ten patients allocated to each prescribing group.

For the outcome of cholesterol control, the only inference that could be made was that pharmacist prescribers can manage cholesterol as well as doctors. One study recruited small patient numbers (14 in total) and no meaningful conclusion could be drawn.[27] In the remaining study, post-trial mean LDL was found to be statistically significantly lower in the intervention group although this difference was not considered clinically significant.[24] The percentage of patients who achieved a target LDL cholesterol of 2.6 mmol/L was also reported. However, this target was above the currently recommended target LDL of less than 1.8 mmol/L in patients with very high cardiovascular risk (i.e. type 2 diabetes), a target thought to provide the best benefit in terms of cardiovascular disease reduction.[60] The study did not report the number of patients who achieved a reduction of at least 50% from baseline, which is also considered an acceptable target in patients at high risk of cardiovascular disease who fail to achieve target LDL of below 1.8 mmol/L.[62]

Adverse events were measured in studies which involved anticoagulant (heparin sodium and warfarin) prescribing and related to bleeding or thromboembolic events.[21,22,29,30,32,34] The quality of evidence for this outcome measure was assessed to be low. While the number of adverse events that occurred in each arm was similar, a meaningful conclusion could not be drawn from these results for a number of reasons. Randomized controlled trials or prospectively controlled quasi experimental trials are not usually designed to detect adverse outcomes.[61,62] This is mainly due to the nature of the trial design, where the adverse outcome may be poorly defined or not the main outcome of interest, there is limited statistical power to detect rare events that occur, and the duration of the study may not be sufficiently long enough to detect the outcome of interest. As the studies on anticoagulant prescribing were conducted to measure efficacy of the intervention, these studies were underpowered to detect the difference in adverse events between groups. This was further compounded by the small number of events that occurred in each arm. Where classification of bleeding events occurred (minor, major, life-threatening), they differed between studies, making comparison across studies difficult.

For the outcome of appropriate warfarin doses prescribed, the quality of evidence was graded as low. The studies included quasi experimental trials which carry a risk of allocation bias; participants or those delivering treatment were not blinded; and included a small number of participants. Pharmacists were found to comply with warfarin guidelines fully (100%), while doctors were found to comply with the guidelines approximately 70% of the time when initiating loading doses and 46% of the time when initiating maintenance doses.[29,30] The finding that pharmacists are better at adhering to guidelines is not surprising, as pharmacists who are authorized to prescribe by protocol can only legally prescribe according to those guidelines. In addition, the pharmacist prescribers in this study were aware that their prescribing was being assessed for appropriateness. Doctors had access to dosing guidelines in both studies but were not obliged to use them in at least one of these studies, while guidelines were used by pharmacists in both studies (although one study allowed deviation from guidelines according to the clinical judgement of the pharmacist). Warfarin nomograms are designed to guide initiation of warfarin therapy but the optimal warfarin dosing regimen has not been firmly established.[63,64] In some cases, a doctor's clinical judgement and experience may be just as effective as warfarin nomograms and hence assessing adherence to these guidelines may not be a good indication of whether INR will be achieved in a desired timeframe.

The studies in this review showed pharmacists were better than doctors at assessing and prescribing VTE prophylaxis in the preadmission clinic.[19] However, this benefit was not apparent when medication charts were assessed on admission, suggesting that prescriptions written by doctors in the preadmission clinic are usually re-assessed, with most errors corrected appropriately at the time of patients' admission to hospital. This may reflect the time pressure that doctors are under when patients are being assessed in the preadmission clinic, with less care being taken for prescribing when the medication chart is not expected to be in use until the patient's admission to hospital, which may be weeks after the time of prescribing.

For the outcome of effectiveness of anticoagulation prescribing (i.e. maintenance of INR in therapeutic range), the evidence was graded as low. The studies included quasi experimental trials which carry a risk of allocation bias and included a small number of participants. International Normalized Ratio was used as a surrogate endpoint for therapeutic effectiveness but the level of evidence was not downgraded as recommended by the GRADE Handbook.[18] This is because there is good evidence to show that INR is correlated with therapeutic effect, bleeding and thromboembolic risk. The optimum therapeutic range for most conditions requiring anticoagulation is well established to be an INR between 2.0 and 3.0. Patients with better INR control are less likely to have bleeding and thromboembolic events.[65] The incidence for major bleeding when INR is greater than 3.0 is doubled compared to when INR is between 2.0 and 3.0.[65] Bleeding rate as a whole doubles as the INR increases from 2.0 – 2.9 to 3.0 – 4.4, quadruples between 4.5 – 6.0 and multiplies by five when INR is above 7.0, with a consistent increase in major bleeding when INR exceeds 4.0 – 5.5.[66]

Previous research indicates that in patients with poor INR control (time in therapeutic range less than 60%), major bleeding and mortality rate is 3.85% and 4.20%, respectively, compared to 1.96% and 1.84% in patients with moderate INR control (time in therapeutic range between 60 – 70%), and 1.58% and 1.69% in patients with good INR control (time in therapeutic range greater than 75%).[67]

International Normalized Ratio as a surrogate endpoint becomes an important measure when bleeding or thromboembolic events are rare and are less useful in studies that are performed short term or recruit small patient numbers.

Thromboembolic events can transpire as the result of failure to anticoagulate patients at risk, or to provide inadequate anticoagulation in patients with established risk factors. Inadequate anticoagulation occurs when anticoagulant doses are insufficient to achieve target values for laboratory markers known to reduce thromboembolic risk, e.g. INR for warfarin and Activated Partial Thromboplastin Time (APTT) for heparin. International Normalized Ratio is considered sub-therapeutic when the value is below 2.0, but studies have shown that the risk of thromboembolism rises most acutely when INR is 1.5 or below.[68,69] Inadequate anticoagulation has been shown to predict higher rates of recurrence of venous thromboembolism.[71]

Overall, the results of the studies assessed in this review indicated a clinically significant difference

between pharmacist and doctor prescribing with a reduced bleeding risk in the pharmacist arm. The key findings from the studies included:

- More time spent in therapeutic range (64% versus 59%), corresponding to an absolute risk reduction for major bleeding and mortality of 1.89% and 2.36%, respectively, in the intervention group based on moderate INR control in the intervention group, compared to poor INR control in the control group.[21]
- Less patients with an INR above 6.0 in the intervention arm (1% versus 5%), where an INR above 6.0 confers a four-fold increase in bleeding risk compared to an INR between 2.0 – 3.0.[28]

In terms of thromboembolic risk, the main conclusion that can be made is that patients in the intervention arm were at lower risk of thromboembolic events. No inference can be made on whether these findings were clinically significant without further information on the range of INR values measured below 2.0.

No studies showed clinically significant differences between arms for the time it took to reach therapeutic range.

In general, pharmacist prescribing was considered appropriate by doctors where this was assessed, as judged by their high agreement with therapeutic plans made by pharmacist prescribers. Caution needs to be used in interpreting this finding as the studies used doctor judgement as the gold standard rather than pre-determined criteria or accepted standards of practice.

Overall, satisfaction surveys conducted indicate that patients are as satisfied with care provided by pharmacist prescribers as with their doctors. One study also found that patients perceived pharmacists to be more accessible and to have spent more time with them during their appointment. This is reflective of general consensus that pharmacists are one of the most accessible healthcare professionals for the general public.[70] While these initial results on satisfaction related to the services provided are promising, the two studies included were conducted more than 10 years ago. During this time, there have been significant changes in the clinical services provided by hospital pharmacists,[71,72] and more up-to-date studies on patient satisfaction with pharmacist prescribing are warranted to reflect current viewpoints.

Benefits of pharmacist prescribing and barriers to implementation

The main benefit of non-medical prescribing is associated with the resultant flexible model of care that can be provided to patients. This can improve patients' accessibility to medications, reduce waiting times and reduce the workload of doctors which may also minimize errors that occur due to high demands on doctors and their other competing priorities.

Pharmacist prescribing may also improve the workflow and efficiency of a patient's hospital journey. For example, medication histories for patients are often taken more than once during their admission to hospital, firstly when being assessed by a doctor in the emergency department, then possibly by a doctor in the admitting unit, and at some stage during hospitalization by a clinical pharmacist. This process can be simplified by having a clinical pharmacist perform a medication history for the patient on admission, and pharmacists prescribing the required medications on a medication chart. This would also negate the need for hospital doctors to prescribe the patient's usual medications prior to admission. Any issues arising regarding medications which may need to be held or ceased on admission can be discussed with the patient's doctor, reducing the potential for inadvertent administration of medications which are no longer required.

This review provides low to moderate evidence that pharmacists are able to prescribe to the same standards as doctors, and when prescribing by protocol, pharmacists are in fact better at adhering to dosing guidelines and make less prescribing errors in terms of charting patients' usual medications on admission to hospital. At least one study also found that pharmacist prescribing was associated with reduced costs in an anticoagulation outpatient clinic, although this was mainly due to the differences in salaries between pharmacists and doctors.[21]

When considering implementation of pharmacist prescribing in hospitals, prescribing by protocol (e.g. warfarin dosing) should be considered first, as this requires less training and expertise compared to other forms of prescribing. Other forms of dependent prescribing could then be considered subsequently for implementation. Collaborative and independent prescribing requires more autonomy, especially if it is not restricted to specific medication classes, and therefore should be considered in

practitioners with either specialist training, experience or expertise in a nominated area.

The perceived barriers to the successful implementation of pharmacist prescribing are well documented in the literature and are mainly related to supplementary, collaborative or independent prescribing models.[75-81]

Doctors have identified the following issues as potential barriers to pharmacist prescribing – feeling that their [doctor] authority is being infringed, pharmacists' awareness [or lack thereof] of clinical and patient details, pharmacists' lack of clinical examination skills, potential communication problems, belief that a doctor should write the initial inpatient prescription and loss of opportunity to review drug treatment.[73-75]

Pharmacists have also identified barriers towards implementation of pharmacist prescribing. Further training (e.g. clinical examination skills, medico-legal aspects) was felt to be required for this additional responsibility, in addition to adequate experience prior to taking on this role, and concerns with the potential extra demands on their time.[76,77]

Patient views on pharmacist prescribing have been generally positive, although patients indicated that they would prefer the doctor to make the initial diagnosis, and for a multidisciplinary team approach to be used in cases involving complex medical conditions.[77-79]

In recognition of some of these barriers discussed above, a framework for non-medical prescribing has been proposed.[4] In this framework, the steps to safe and competent prescribing have included compulsory accredited education and training, recognition of prescribing competency from the relevant governing body of the health profession, authorization to prescribe by relevant legislation and regulations, prescription of medications within the scope of practice and the maintenance of competency to prescribe.

Limitations of the studies

The studies included in this review were conducted in different settings – inpatients, outpatients and preadmission clinics. Each hospital setting is associated with different pharmacy prescribing foci. For example, outpatient clinics usually cater for patients with a specific medical condition such as hypertension or patients on warfarin which limits the prescribing activities of a pharmacist, while prescribing activities in a preadmission clinic are usually related to medications patients were taking prior to admission and consideration of venous thromboembolism prophylaxis. When considering the applicability of the findings in this review in clinical practice, both the specific outcome and the hospital setting in which the study was conducted should be taken into account.

In addition to only a limited number of studies of high quality being identified, a high proportion of the studies only recruited small numbers of patients. Caution needs to be exercised when considering the clinical significance of the results due to small patient numbers.

In a number of studies, the methodology of the study was poorly reported or lacking in detail. In others, statistical analysis was either not made or the method used was not specified. The majority of studies did not report power and sample size analyses and studies which found no difference between arms may have lacked power to detect statistically significant differences. The lack of transparency in the reporting of these issues is a concern as there is a risk the studies were not well designed and prone to bias. Another bias that requires consideration is that most of the studies were designed by a pharmacist, with data collection and data analysis performed by the same pharmacist. There is a risk that the study design was biased towards a positive finding, and that negative findings were not reported. For example, in one study, patients in the intervention arm had their medication history taken in the preadmission clinic, while patients in the control arm were contacted by telephone following discharge, possibly resulting in a recall bias by patients and a distortion of the results of the study.[25]

There was also significant heterogeneity in the outcome measures that were reported between studies. For example, when reporting on INR control, the studies reported on patient time or percentage of INRs or patients in a specified range. In cases where the outcome measure was consistent across studies, there was variation in the definition of the outcome measure. For example, where bleeding was reported as an adverse event, it was further subdivided into major or minor bleeding in some studies, but different definitions were used for these events. These differences in reporting meant that data pooling in a meta-analysis was not possible.

Studies that reported on therapeutic failure or benefit as an outcome measure did not account for differences in baseline measures between arms,[23,24,26] while other studies did not adjust for patient mix.[19,23,26] Of the three studies which had statistically significant differences between mean baseline measures between groups, only one study adjusted for this difference using an ANCOVA.[23] Due to the potential for over- or under-estimation of the intervention effect when there is a difference in baseline measures between groups, ANCOVA has been recommended as the preferred statistical analysis for trials with baseline and follow up measurement.[36]

In a simulation study, ANCOVA has been found to have generally greater statistical power in detecting a treatment effect compared to other methods.[80] The failure to account for the difference in study population between arms makes it difficult to interpret the study findings and consequently no definitive conclusions could be made.

Although statistical significance was reported for some studies, a more relevant measure of effectiveness, the clinical significance of the findings, was not discussed in any of the included studies. Studies with large sample sizes may report a statistically significant difference between groups which are not clinically important.

Other limitations were also present in the studies included in the review. This included the level of experience of clinicians being compared between arms (experienced pharmacists versus junior doctors), and the definition of what was considered appropriate prescribing. Medications were considered to be prescribed appropriately if they could be reconciled with the patient's medication list prior to admission. However, this does not necessarily constitute appropriate prescribing if medications that are no longer appropriate for the patient (due to factors such as change in a patient's disease state or organ function) are not reviewed and consequently continue to be prescribed.

Limitations of the review

This review aimed to include studies performed in the hospital setting, but this proved to be more challenging than originally anticipated. In the USA, the healthcare system is unique in that it is provided by various organizations such as the government, health insurance providers and not-for-profit establishments. Healthcare in the USA is provided in settings ranging from hospitals, health maintenance organizations, medical centers, Veterans Affairs Medical Centers (VAMC) and university affiliated outpatient clinics. The distinction between a specialist medical center with the capacity to admit patients and a hospital in the traditional sense was not straightforward. This review included all papers which specifically stated the studies were conducted in a hospital setting. Where a hospital setting was not specified, studies were included if they met the definition of a hospital according to the World Health Organization, that is, "hospitals are health care institutions that have an organized medical and other professional staff, and inpatient facilities, and deliver services 24 hours per day, 7 days per week. They offer a varying range of acute, convalescent and terminal care using diagnostic and curative services."[81[para.1]] Studies that were performed in outpatient clinics but did not specifically state their affiliation to a hospital were excluded. Based on these criteria, studies may be considered to have been included or excluded inappropriately by persons more familiar with the nomenclature used in the description of healthcare settings in the USA.

A systematic search was conducted across multiple databases (including one for gray literature) to ensure that all relevant studies were identified. However, it is still possible that some articles were missed in this process. The largest limitation in the search methodology was the lack of medical subject heading for "pharmacist prescribing", which necessitated searching for the two keywords separately. This resulted in retrieval of a large number of articles which required screening to determine inclusion or exclusion in this review. The large volume of articles, which was screened by a sole reviewer, increased the possibility that relevant studies were not identified and omitted from this review. While two reviewers critically appraised the studies identified for inclusion, only one reviewer performed data extraction (in duplicate), increasing the risk for errors. In addition, only studies in English were considered for inclusion, introducing a language bias in this review.

The high level of heterogeneity between the studies included in the review meant that statistical pooling of data in a meta-analysis was not possible. Consequently, only a general statement that pharmacist prescribing has been shown to be just as effective as doctors can be made.

It should also be highlighted that prescribing is often not the sole activity that is being performed by the pharmacist or doctor, with pharmacists performing inherently different activities to doctors. For example, prior to prescribing, a pharmacist may be more focused on medication history-taking, medication reconciliation and medication review, while a doctor may be more concerned with medical examination and clinical diagnosis. Additionally, pharmacists are more likely to provide patients with medication counselling when writing a prescription. These additional activities cannot be separated from the act of prescribing for each of the professions and their effects on prescribing outcomes have not been accounted for in this review. Similarly, in some studies in this review, there may have been slight variations in the intervention studied, for example, a different duration between follow-up appointments in the two groups or patients offered additional lifestyle modification advice in one arm. These differences could have influenced the study outcomes.

All the studies measuring therapeutic failure or benefit as an outcome used surrogate endpoints as the measure of effectiveness of therapy. Surrogate endpoints used in the studies included in this review were blood pressure (systolic and diastolic), cholesterol (low density lipoprotein and total cholesterol), blood sugar levels and HbA1c. The level of evidence was not downgraded for indirectness in this review as improvement in these endpoints are well established to be correlated with reduction of cardiovascular events including stroke, myocardial infarction and mortality. While this was considered appropriate for this review, it may also be considered a limitation as it is in contradiction to the recommendations of the GRADE approach.[18]

The clinical significance of the findings were discussed in the review and derived from primary literature, where possible. However, as clinical judgement (which is subjective) is required to determine whether an intervention is clinically significant, other stakeholders may have differing views on whether the findings of a study is significant enough to warrant a change in clinical practice.

Conclusion

Overall, the studies included in this review indicate that pharmacist prescribing is non-inferior to doctor prescribing in all measured outcomes of interest. This included the prescription of medications to manage blood pressure, diabetes and cholesterol; the prescription of heparin sodium and warfarin according to dosing nomograms; and the prescription of patients' usual medications on admission to hospital. Pharmacists performed better than doctors in several aspects of prescribing, specifically in the accuracy of prescribing a patient's usual medication regimen on admission and in adhering to dosing nomograms.

Recommendations for practice

Pharmacists are less likely than doctors to make prescribing errors or omit medications from the medication chart when prescribing medications for patients on admission to hospital. Based on the results of this review, it is recommended that, as part of their scope of practice, hospital pharmacists prescribe a patient's existing medications during the patient's initial presentation to hospital (including in the preadmission clinic), conditional upon the use of the supplementary prescribing model (Grade B). Pharmacists are non-inferior to doctors when prescribing medications to reduce the risk of cardiovascular disease, particularly in the management of hypertension, diabetes and cholesterol. It is recommended that hospital pharmacists prescribe medications for the management of blood pressure, diabetes or cholesterol in hospital outpatient clinics, conditional upon this prescribing being consistent with dependent or collaborative prescribing models (Grade B). When prescribing anticoagulants according to protocol, the evidence shows pharmacists maintain INR in therapeutic range just as well as doctors; this is also reflected in the similar number of adverse events between arms. The evidence also shows pharmacists prescribe warfarin doses according to warfarin nomograms more accurately than doctors. It is recommended that hospital pharmacists prescribe anticoagulants (specifically heparin and warfarin) for patients in the inpatient and outpatient setting, conditional upon this prescribing being in accord with dosing nomograms (Grade B).[82]

Recommendations for research

This review did not identify any studies which used an independent prescribing model. Future research should consider the effectiveness of pharmacist prescribing with this more autonomous model of prescribing as it may be beneficial in some areas of practice, such as in remote areas with less access to

medical care. No studies were found assessing pharmacist prescribing in children or adolescents (under 18 years of age). Future research should also include this age group in the study design. There was a lack of studies focusing on specific clinical areas such as mental health, respiratory conditions, infectious diseases and obstetrics; future research should consider these clinical domains.

This review further highlighted a lack of research in pharmacist prescribing with a specific focus on clinical outcomes such as morbidity, mortality and adverse events. Studies that reported mortality and adverse events as secondary outcomes were insufficiently powered to detect a clinically important difference between arms. Future research should include adequately powered, rigorously conducted and methodologically sound RCTs that address this research gap. Surrogate endpoints such as blood pressure and cholesterol control remain important measures of effectiveness of the intervention but should be measured in conjunction with clinical outcomes of interest such as morbidity, mortality, hospital admissions and cardiovascular events. While this review did not consider healthcare cost as a patient-related outcome, it highlighted a lack of methodologically sound studies which included economic assessments. Future research should consider comparing healthcare costs between pharmacist and doctor prescribing.

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References

1. Hoti K, Hughes J, Sunderland B. An expanded prescribing role for pharmacists - an Australian perspective. Australas Med J 2011;4(4):236–42.
2. Tonna AP, Stewart D, West B, McCaig D. Pharmacist prescribing in the UK - a literature review of current practice and research. J Clin Pharm Ther 2007;32(6):545–56.
3. Bhanbhro S, Drennan VM, Grant R, Harris R. Assessing the contribution of prescribing in primary care by nurses and professionals allied to medicine: a systematic review of literature. BMC Health Serv Res 2011;11:330.
4. Heath Workforce Australia 2013. Health Professionals Prescribing Pathway (HPPP) Project – Final Report. [Internet]. [Cited 20 Apr 2015]. Available from: http://www.hwa.gov.au/sites/uploads/HPPP-Final-Report-November-2013.pdf.
5. Nissen L, Kyle G, Stowasser DA, Lum E, Jones A, McLean C, et al. Non-Medical Prescribing. Australian Health Workforce Institute, Collaboration NHW-Par.2010. [Internet]. [Cited 20 Apr 2015]. Available from: http://www.ahwo.gov.au/documents/NHWT/Non%20Medical%20Prescribing%20Final%20Report.pdf.
6. Emmerton L, Marriott J, Bessell T, Nissen L, Dean L. Pharmacists and prescribing rights: review of international developments. J Pharm Pharmaceut Sci 2005;8(2):217–25.
7. Stewart D. Pharmacist prescribing: A view from the UK. J Pharm Pract Res 2009;39(1):7–10.
8. Gielen SC, Dekker J, Francke AL, Mistiaen P, Kroezen M. The effects of nurse prescribing: A systematic review. Int J Nurs Stud 2014;51(7):1048–61.
9. Kroezen M, Dijk L, Groenewegen P, Francke A. Nurse prescribing of medicines in Western European and Anglo-Saxon countries: a systematic review of the literature. BMC Health Serv Res 2011;11(127):1–42.
10. Weeks G, George J, Maclure K, Stewart D. Non-medical prescribing versus medical prescribing for acute and chronic disease management in primary and secondary care. Cochrane Database Syst Rev 2016;11:CD011227.
11. Kay OC, Brien JE. Pharmacist Prescribing: Review of the Literature. J Pharm Pract Res 2004;34(4):300–4.
12. Finley PR, Crismon ML, Rush AJ. Evaluating the Impact of Pharmacists in Mental Health: A Systematic Review. Pharmacother 2003;23(12):1634–44.
13. Cooper RJ, Anderson C, Avery T, Bissell P, Guillaume L, Hutchinson A, et al. Nurse and pharmacist supplementary prescribing in the UK–a thematic review of the literature. Health Policy 2008;85(3):277–92.
14. Poh EW, McArthur A, Roughead L. The effects of pharmacist prescribing on patient outcomes in the hospital setting: a systematic review protocol. JBI Database System Rev Implement Rep 2016;13(12):4–13.
15. The Joanna Briggs Institute. JBI SUMARI 2017. [internet]. [cited 2018 March 01]. Available from: https://www.jbisumari.org/. Accessed February 26, 2018.
16. The Joanna Briggs Institute. Joanna Briggs Institute Reviewers' Manual: 2017 edition. Australia: The Joanna Briggs Institute; 2017. [Cited 13 Mar 2017]. Available from https://reviewersmanual.joannabriggs.org/.
17. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). [Cited 13 Mar 2017]. Available from gradepro.org.
18. Schunemann H, Brozek J, Oxman A, editors. GRADE Handbook for grading quality of evidence and strength of recommendation. [updated October 2013]. The GRADE Working Group 2013; [internet]. [cited 2017 August 11]. Available from: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.ygojbnr1bi5y.
19. Hale AR, Coombes ID, Stokes J, McDougall D, Whitfield K, Maycock E, et al. Perioperative medication management: expanding the role of the preadmission clinic pharmacist in a single centre, randomised controlled trial of collaborative prescribing. BMJ Open 2013;3(7):e003027.

20. Hale A, Martin J, Coombes I, McDougall D, Coombes J, Nissen L. A pilot study to assess the appropriateness of prescribing from a collaborative pharmacist prescribing study in a surgical pre admission clinic. J Pharma Care Health Sys 2014;1(3):1–6.

21. Chan FWH, Wong RSM, Lau WH, Chan TYK, Cheng G, You JHS. Management of Chinese patients on warfarin therapy in two models of anticoagulation service – a prospective randomized trial. Br J Clin Pharmacol 2006;62(5):601–9.

22. Chenella FC, Klotz TA, Gill MA, Kern JW, McGhan WF, Paulson YJ, et al. Comparison of physician and pharmacist management of anticoagulant therapy of inpatients. Am J Hosp Pharm 1983;40(10):1642–5.

23. Hawkins DW, Fiedler FP, Douglas HL, Eschbach RC. Evaluation of a clinical pharmacist in caring for hypertensive and diabetic patients. Am J Hosp Pharm 1979;36(10):1321–5.

24. Jacobs M, Sherry PS, Taylor LM, Amato M, Tataronis GR, Cushing G. Pharmacist assisted medication program enhancing the regulation of diabetes (PAMPERED) study. J Am Pharm Assoc 2012;52(5):613–21.

25. Marotti SB, Kerridge RK, Grimer MD. A randomized controlled trial of pharmacist medication histories and supplementary prescribing on medication errors in postoperative medications. Anaesth Intensive Care 2011;39(6):1064–70.

26. Vivian EM. Improving blood pressure control in a pharmacist-managed hypertension clinic. Pharmacotherapy 2002;22(12):1533–40.

27. Weeks GR, Fyfe R. Hospital pharmacist-led lipid clinic for surgical patients with peripheral vascular disease at a regional Australian hospital. J Pharm Pract Res 2012;42(1):17–21.

28. Boddy C. Pharmacist involvement with warfarin dosing for inpatients. Pharm World Sci 2001;23(1):31–5.

29. Burns N. Evaluation of warfarin dosing by pharmacists for elderly medical in-patients. Pharm World Sci 2004;26(4):232–7.

30. Damaske D, Baird RW. Development and implementation of a pharmacist-managed inpatient warfarin protocol. Proc (Bayl Univ Med Cent) 2005;18(4):397–400.

31. Pawloski SJ, Kersh PL. Therapeutic heparin monitoring service in a small community hospital. Hosp Pharm 1992;27(8):703–6; 723.

32. Schillig J, Kaatz S, Hudson M, Krol GD, Szandzik EG, Kalus JS. Clinical and safety impact of an inpatient pharmacist-directed anticoagulation service. J Hosp Med 2011;6(6):322–8.

33. Tong EY, Roman C, Mitra B, Yip G, Gibbs G, Newnham H, et al. Partnered pharmacist charting on admission in the general medical and emergency short-stay unit – a cluster-randomised controlled trial in patients with complex medication regimens. J Clin Pharm Ther 2016;41(4):414–8.

34. Chau T, Rotbard M, King S, Li MM, Leong WA. Implementation and evaluation of a warfarin dosing service for rehabilitation medicine: Report from a pilot project. Can J Hosp Pharm 2006;59(3):136–47.

35. Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure, The Sixth Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. National Institutes of Health – National heart, lung, and blood institute. 1997 [cited 15 Mar 2017]. Available from: https://www.nhlbi.nih.gov/files/docs/guidelines/jnc6_archive.pdf.

36. Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. BMJ 2001;323(7321):1123–4.

37. Latter S, Maben J, Myall M, Young A. Evaluating the clinical appropriateness of nurses' prescribing practice: method development and findings from an expert panel analysis. Qual Safe Health Care 2007;16(6):415–21.

38. Society of Hospital Pharmacists of Australia. Standards of Practice for clinical pharmacy services: Documenting clinical activities 2016. S42-S46; [internet]. [cited 2017 July 3]. Available from: https://www.shpa.org.au/resources/standards-of-practice-for-clinical-pharmacy-services.

39. Velo G, Minuz P. Medication errors: prescribing faults and prescription errors. Br J Clin Pharmacol 2009;67(6):624–8.

40. Alanazi MA, Tully MP, Lewis PJ. A systematic review of the prevalence and incidence of prescribing errors with high-risk medicines in hospitals. J Clin Pharmacy Ther 2016;41(3):239–45.

41. Coombes ID, Stowasser DA, Coombes JA, Mitchell C. Why do interns make prescribing errors? A qualitative study. MJA 2008;188(2):89–94.

42. Dean B, Schachter M, Vincent C, Barber N. Causes of prescribing errors in hospital inpatients: a prospective study. Lancet 2002;359(9315):1373–8.

43. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care. Arch Int Med 2006;166(9):955–64.

44. Rosenthal M, Hall KW, Bussieres JF, Tsuyuki RT. Professional culture and personality traits of hospital pharmacists across Canada: A fundamental first step in developing effective knowledge translation strategies. Can J Hosp Pharm 2015;68(2):127–35.

45. Hall J, Rosenthal M, Family H, Sutton J, Hall K, Tsuyuki R. Personality traits of hospital pharmacists: Toward a better understanding of factors influencing pharmacy practice change. Can J Hosp Pharm 2013;66(5):289–95.

46. Aronson JK. Biomarkers and surrogate endpoints. Br J Clin Pharmacol 2005;59(5):491–4.

47. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.

48. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001;358(9290):1305–15.

49. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265(24):3255–64.

50. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977–86.

51. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352(9131):837–53.

52. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). Br Med J 1998;317(7160):703–13.

53. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 39). Br Med J 1998;317(7160):713–20.

54. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52(11):2288–98.

55. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373(9677):1765–72.

56. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassai B, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ 2011;343:d4169.

57. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet 2010;376(9753):1670–81.

58. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360(9326):7–22.

59. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364(9435):685–96.

60. The Task Force for the management of dyslipiademias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2011; 32: 1769-1818. [internet]. [cited 2017 July 31]. Available from: https://www.escardio.org/static_file/Escardio/Guidelines/publications/DYSLIPguidelines-dyslipidemias-FT.pdf.

61. Singh S, Loke YK. Drug safety assessment in clinical trials: methodological challenges and opportunities. Trials 2012;13:138.

62. Tsang R, Colley L, Lynd LD. Inadequate statistical power to detect clinically significant differences in adverse event rates in randomized controlled trials. J Clin Epidemiol 2009;62(6):609–16.

63. Garcia P, Ruiz W, Munarriz CL. Warfarin nomograms for venous thromboembolism. Cochrane Database Syst Rev 2016;1:CD007699.

64. Mahtani KR, Heneghan CJ, Nunan D, Bankhead C, Keeling C, Ward AM, et al. Optimal loading dose of warfarin for the initiation of oral anticoagulation. Cochrane Database Syst Rev 2012;12:CD008685; 10.1002/14651858.CD008685.pub2.

65. Schulman S, Beyth RJ, Keasron C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(Suppl 6):257S–98S.

66. Gallus AS, Baker RI, Chong BH, Ockelford PA. Consensus guidelines for warfarin therapy: Recommendations from the Australasian Society of Thrombosis and Haemostasis. MJA 2000;172(12):600–5.

67. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med 2007;167(3):239–45.

68. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with non-rheumatic atrial fibrillation. NEJM 1996;335(8):540–6.

69. Palareti G, Legnani C, Cosmi B, Guazzaloca G, Cini M, Mattarozzi S. Poor anticoagulation quality in the first 3 months after unprovoked venous thromboembolism is a risk factor for long-term recurrence. J Thromb Haemost 2005;3(5):955–61.

70. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. A program guide for public health: Partnering with the pharmacist in the prevention and control of chronic diseases 2012; [internet]. [cited 2017 May 31]. Available from: http://pubs.lib.umn.edu/cgi/viewcontent.cgi?article=1216&context=innovations.

71. Carter B. Evolution of clinical pharmacy in the USA and future directions for patient care. Drugs and Aging 2016;33(3):169–77.

72. Abramowitz PW. The evolution and metamorphosis of the pharmacy practice model. Am J Health-Syst Pharm 2009;66(16):1437–46.

73. Child D, Cantrill JA. Hospital doctors' perceived barriers to pharmacist prescribing. Int J Pharm Pract 1999;7(4):230–7.

74. Sciberras J, Said E, Cordina M. Perceptions of physicians and pharmacists on hospital physician-pharmacist collaboration: A qualitative insight. Int J Clin Pharm 2013;35(5):859.

75. Stewart DC, George J, Bond CM, Diack HL, McCaig DJ, Cunningham S. Views of pharmacist prescribers, doctors and patients on pharmacist prescribing implementation. Int J Pharm Pract 2009;17(2):89–94.

76. Hoti K, Sunderland B, Hughes J, Parsons R. An evaluation of Australian pharmacists' attitudes on expanding their prescribing role. Pharm World Sci 2010;32(5):610–21.

77. McIntosh T, Munro K, Stewart D, McLay J. What do newly qualified pharmacists in Britain think about possible future roles as pharmacist prescribers? Int J Pharm Pract 2010;18(1):27–8.

78. McCann LM, Haughey SL, Parsons C, Lloyd F, Crealey G, Gromley GJ, *et al*. A patient perspective of pharmacist prescribing: "crossing the speacialisms-crossing the illness-ness". Health Expect 2015;18(1):58–68.

79. Hoti K, Hughes J, Sunderland B. Pharmacy client's attitudes on expanded pharmacist prescribing and the role of agency theory on involved stakeholders. Int J Pharm Pract 2011;19(1):5–12.

80. Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. BMC Med Res Methodol 2001;1:6.

81. World Health Organization. Hospitals; [internet]. [cited 2017 August 8]. Available from: http://www.who.int/hospitals/en/.

82. The Joanna Briggs Institute Levels of Evidence and Grades of Recommendation Working Party. Supporting document for the Joanna Briggs Institute levels of evidence and grades of recommendation. Adelaide, Australia: The Joanna Briggs Institute; 2016. [Cited 5 Sept 2017]. Available from: www.joannabriggs.org/jbi-approach.html#tabbed-nav=Grades-of-Recommendation.

Appendix I: Search strategy

Pubmed: 24/1/17

No.	Search terms	No. results
1	Pharmacists[mh] OR pharmacist*[tw] OR clinical pharmacy[tw]	29,701
2	Pharmaceutical services[mh] OR pharmaceutical service*[tw] OR pharmacy service*[tw] OR pharmaceutical care*[tw] OR pharmacy service, hospital[mh] OR pharmacy[mh] OR pharmacy[tw] OR hospital pharmacy[tw]	93,392
3	Drug prescriptions[mh] OR prescription*[tw] OR prescribe*[tw] OR prescribing*[tw]	177,968
4	Hospitals[mh] OR hospital*[tw] OR secondary care[tw] OR secondary health care[tw] OR tertiary care[tw] OR tertiary health care[tw] OR outpatients[mh] OR outpatient*[tw] OR ambulatory care[mh] OR ambulatory care facilities[mh] OR ambulatory care[tw] OR ambulatory service[tw] OR emergency service, hospital[mh] OR emergency service*[tw] OR emergency department*[tw] or emergency room[tw] OR emergency ward*[tw] OR emergency unit*[tw] or accident and emergenc*[tw] OR perioperative period[mh] OR perioperative[tw] OR perioperative care[mh] OR intraoperative[tw] OR preoperative[tw] OR elective surgical procedures[mh] or elective surg*[tw]	1,894,359
5	(#1 or #2) AND #3 AND #4	10,968
6	Limit #6 to English	9597

Embase: 24/1/17

No.	Search terms	No. results
1	Pharmacist:de OR pharmacist*:ti,ab OR "clinical pharmacy":de OR "clinical pharmacy":ti,ab	84,682
2	"hospital pharmacy":de OR "hospital pharmacy":ti,ab OR "hospital pharmacy service":ti,ab OR pharmacy:de OR pharmacy:ti,ab OR "pharmaceutical service":ti,ab OR "pharmaceutical services":ti,ab OR "pharmacy service":ti,ab OR "pharmacy services":ti,ab OR "pharmaceutical care":ti,ab	110,537
3	Prescription:de OR prescription*:ti,ab OR prescribing:ti,ab OR prescribe*:ti,ab	306,207
4	Hospital/exp OR hospital*:ti,ab OR "secondary health care"/exp OR "secondary care":ti,ab OR "secondary health care":ti,ab OR "tertiary health care"/exp OR "tertiary health care":ti,ab OR "tertiary care":ti,ab OR outpatient:de OR outpatient*:ti,ab OR "ambulatory care"/exp OR "ambulatory care":ti,ab OR "ambulatory service":ti,ab OR "emergency health service":de OR "emergency service":ti,ab OR "emergency services":ti,ab OR "emergency department":ti,ab OR "emergency room":ti,ab OR "emergency ward":ti,ab OR "emergency unit":ti,ab OR "accident and emergency":ti,ab OR "accident and emergencies":ti,ab OR "perioperative period":de OR perioperative:ti,ab OR intraoperative:ti,ab OR preoperative:ti,ab OR "elective surgery":de OR "elective surgery":ti,ab OR "elective surgeries":ti,ab	2,459,708
5	#1 or #2	151,837
6	#3 AND #4 AND #5	13,826
7	Limit #6 to English	12,113

CINAHL: 24/1/17

No.	Search terms	No. results
1	MH pharmacists OR TI pharmacist* OR AB pharmacist* OR TI "clinical pharmacy" OR AB "clinical pharmacy"	9108
2	MH pharmacy service+ OR TI "hospital pharmacy" OR AB "hospital pharmacy" OR TI "hospital pharmacy service" OR AB "hospital pharmacy service" OR TI pharmacy OR AB pharmacy OR TI "pharmaceutical service*" OR AB "pharmaceutical service*" OR TI "pharmaceutical care" OR AB "pharmaceutical care"	10,602
3	MH medication prescribing OR TI prescribing OR AB prescribing OR TI prescribe* OR AB prescribe* OR MH prescriptions, drug OR TI prescription* OR AB prescription* OR MH prescriptions, non-drug	38,662
4	MH hospitals+ OR TI hospital* OR AB hospital* OR MH secondary health care OR TI "secondary health care" OR AB "secondary health care" OR TI "secondary care" OR AB "secondary care" OR MH tertiary health care OR TI "tertiary health care" OR AB "tertiary health care" OR TI "tertiary care" OR AB "tertiary care" OR MH outpatient service OR TI outpatient* OR AB outpatient* OR MH outpatients OR MH ambulatory care facilities+ OR TI "ambulatory care" OR AB "ambulatory care" OR TI "ambulatory service" OR AB "ambulatory service" OR MH emergency service+ OR TI "emergency service*" OR AB "emergency service*" OR TI "emergency department" OR AB "emergency department OR TI "emergency room" OR AB "emergency room" OR TI "emergency ward" OR AB "emergency ward" OR TI "emergency unit" OR AB "emergency unit" OR TI "accident and emergenc*" OR AB "accident and emergenc*" OR MH perioperative care+ OR MH preoperative period+ OR TI perioperative OR AN perioperative OR TI intraoperative OR AB intraoperative OR TI preoperative OR AB preoperative OR MH surgery, elective+ OR TI "elective surger*" OR AB "elective surger*"	362,825
5	#1 OR #2	16,105
6	#3 AND #4 AND #5	1139
7	Limit #6 to English	1055

Cochrane Central Register of Controlled Trials: 24/1/17

No.	Search terms (searched in title, abstract or as keywords)	No. results
1	Pharmacist OR "clinical pharmacy"	3927
2	"pharmacy service" OR "hospital pharmacy" OR "hospital pharmacy service" OR pharmacy OR "pharmaceutical service" OR "pharmaceutical care"	11,586
3	"medication prescribing" OR prescribing OR prescribe* OR "drug prescription" OR prescription*	19,749
4	Hospital* OR "secondary health care" OR "secondary care" OR "tertiary health care" OR "tertiary care" OR "outpatient service" OR outpatient* OR "ambulatory care facilities" OR "ambulatory care" OR "ambulatory service" OR "emergency service" OR "emergency department" OR "emergency room" OR "emergency ward" OR "emergency unit" OR "accident and emergency" OR "perioperative care" OR "preoperative period" OR perioperative OR intraoperative OR "elective surgery"	252,227
5	#1 OR #2	12,729
6	#3 AND #4 AND #5	1808
7	Limit #6 to Trials	460

Scopus: 24/1/17

No.	Search terms	No. results
1	Pharmacist OR "clinical pharmacy"	76,396
2	"Pharmacy service*" OR "hospital pharmacy" OR "hospital pharmacy service" OR pharmacy OR "pharmaceutical service*" OR "pharmaceutical care"	123,586
3	"Medication prescribing" OR prescribing OR prescribe* OR "drug prescription" OR prescription	348,811
4	Hospital* OR "secondary health care" OR "secondary care" OR "tertiary health care" OR "tertiary care" OR "outpatient service*" OR outpatient* OR "ambulatory care facilit*" OR "ambulatory care" OR "ambulatory service*" OR "emergency service*" OR "emergency department" OR "emergency room" OR "emergency ward" OR "emergency unit" OR "accident and emergency" OR "perioperative care" OR "preoperative period" OR perioperative OR intraoperative OR "elective surger*"	2,274,309
5	#1 OR #2	158,029
6	#3 AND #4 AND #5	11,647
7	Limit #6 to English	9852

Web of Science Core Collection: 24/1/17

No.	Search terms	No. results
1	pharmacist OR "clinical pharmacy"	*
2	"Pharmacy service*" OR "hospital pharmacy" OR "hospital pharmacy service" OR pharmacy OR "pharmaceutical service*" OR "pharmaceutical care"	*
3	"Medication prescribing" OR prescribing OR prescribe* OR "drug prescription" OR prescription	*
4	Hospital* OR "secondary health care" OR "secondary care" OR "tertiary health care" OR "tertiary care" OR "outpatient service*" OR outpatient* OR "ambulatory care facilit*" OR "ambulatory care" OR "ambulatory service*" OR "emergency service*" OR "emergency department" OR "emergency room" OR "emergency ward" OR "emergency unit" OR "accident and emergency" OR "perioperative care" OR "preoperative period" OR perioperative OR intraoperative OR "elective surger*"	*
5	(#1 OR #2) AND #3 AND #4	*
6	Limit #5 to English	6978

*Exact number not available – database only offers approximately numbers until duplicates are removed when the final page of the search result is viewed.

MedNar: 24/1/17

No.	Search terms	No. results
1	Pharmacist prescribing	1802

Google Scholar: 24/1/17

No.	Search terms	No. results
1	Hospital "Pharmacist prescribing"	1200

Appendix II: Excluded studies and reasons for their exclusion

Abutaleb MHA. Clinical comparative effectiveness of independent non-medical prescribers for type 2 diabetes. 2015.
Reason for exclusion: Not a controlled study – observational, retrospective design

Adams GW. Parenteral nutrition collaborative drug therapy management service. Hosp Pharm. 2000;35(11):1242–8.
Reason for exclusion: Not a study – narrative only

Albsoul-Younes AM HE Yasein NA, Tahaineh LM. Pharmacist-physician collaboration improves blood pressure control. Saudi Med J. 2011;32(3):288–92.
Reason for exclusion: Does not involve pharmacist prescribing

Baqir W CJ Smith J. Evaluating pharmacist prescribing across the North East of England. Br J Clin Pharm. 2010;2:147–9.
Reason for exclusion: Not a controlled study – observational design

Bhanji AA FK LeBlanc SP. Pharmacy involvement in a surgery preadmission program. Am J Hosp Pharm. 1993;50(3):483–6.
Reason for exclusion: Not pharmacist prescribing

Bunz D GS Jewesson P. Metronidazole cost containment: a two-stage intervention. Hosp Formul. 1990;25(11):1167–9, 1177.
Reason for exclusion: Not considered pharmacist prescribing – changing dosing interval from 8 hourly to 12 hourly using pre-stamped form; pre-test post-test study

Cao BY CC Elliott P, MacPherson RD, Crane J, Bajorek BV. Implementing a Pharmacist Charting Service in the PreAdmission Clinic. J Pharm Pract Res. 2011;41(2):102–7.
Reason for exclusion: Not a controlled study – pre-test post-test study

Cattell R CC Sheikh A. Pharmacist integration into the discharge process: A qualitative and quantitative impact assessment. Int J Pharm Pract. 2001;9(1):59–64.
Reason for exclusion: Not pharmacist prescribing – transcribing only

Chantelois EP SN. A pilot program comparing physician- and pharmacist-ordered discharge medications at a Veterans Affairs Medical Center. Am J Health Syst Pharm. 2003;60(16):1652–6.
Reason for exclusion: Not pharmacist prescribing – transcribing only

Chiquette E AM Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. Arch Intern Med. 1998;158(15):1641–7.
Reason for exclusion: Not hospital setting

Clifford RM BK Davis TME, Davis W, Stein G, Stewart G, Plumridge RJ. A randomised controlled trial of a pharmaceutical care programme in high-risk diabetic patients in an outpatient clinic. Int J Pharm Pract. 2002;10(2):85–9.
Reason for exclusion: Not pharmacist prescribing

Choe HM KJ Choi KE, Mueller BA. Implementation of the first pharmacist-managed ambulatory care anticoagulation clinic in South Korea. Am J Health Syst Pharm. 2002;59(9):872–4.
Reason for exclusion: Not a peer reviewed article – narrative form only

Culshaw M DS. Assessing the value of a discharge pharmacist. Pharm Manage. 1998;14(2):22–3.
Reason for exclusion: Not a controlled study

D'Achille KM SL Hill WT Jr. Pharmacist-managed patient assessment and medication refill clinic. Am J Hosp Pharm. 1978;35(1):66–70.

Reason for exclusion: Not a controlled study – pre-test post-test

Entezari-Maleki T DS Hamishehkar H, Gholami K. A systematic review on comparing 2 common models for management of warfarin therapy; Pharmacist-led service versus usual medical care. Journal of Clinical Pharmacology. 2016;56(1):24–38.
Reason for exclusion: Only includes studies in the outpatient setting

Erickson SH. Primary care by a pharmacist in an outpatient clinic. Am J Hosp Pharm. 1977;34(10):1086–90.
Reason for exclusion: Not hospital setting

Feetam C NG. Pharmacist prescribing in mental health. Hosp Pharmacist - London. 2004;11(2):76–7.
Reason for exclusion: Not a study – narrative only

Fox ER BM Tyler LS. Pharmacy-administered IV to oral therapeutic interchange program: Development, implementation, and cost-assessment. Hosp Pharm. 2003;38(5):444–452+462.
Reason for exclusion: Not considered pharmacist prescribing

Gray DR G-RS Chretien SD. Cost-justification of a clinical pharmacist-managed anticoagulation clinic. Drug Intell Clin Pharm. 1985;19(7–8):575–80.
Reason for exclusion: Not a controlled study – pre-test post-test

Haag JD DA Hoel RW, Armon JJ, Odell LJ, Dierkhising RA, Takahashi PY. Impact of Pharmacist-Provided Medication Therapy Management on Healthcare Quality and Utilization in Recently Discharged Elderly Patients. Am Health Drug Benefits. 2016;9(5):259–68.
Reason for exclusion: Not pharmacist prescribing – made recommendations only

Hale AR. Doctor-Pharmacist Collaborative Prescribing in a Multidisciplinary Surgical Preadmission Clinic: Expanding the Role of the Preadmission Clinic Pharmacist. 2014;
Reason for exclusion: Same information presented in other two papers included for critical appraisal

Hale A CI Stokes J, Aitken S, Clark F, Nissen L. Patient satisfaction from two studies of collaborative doctor - pharmacist prescribing in Australia. Health Expect. 2016;19(1):49–61.
Reason for exclusion: Not true randomization – control arm did not participate in satisfaction survey (no comparator)

Hick HL, Deady PE, Wright DJ, Silcock J. The impact of the pharmacist on an elective general surgery pre-admission clinic. Pharmacy World and Science. 2001;23(2):65–9.
Reason for exclusion: Not pharmacist prescribing – transcribing only

Hwang S, Koleba T, Mabasa VH. Assessing the impact of an expanded scope of practice for pharmacists at a community hospital. The Canadian journal of hospital pharmacy. 2013;66(5).
Reason for exclusion: Not a controlled study – retrospective design

Jarab AS, Alqudah SG, Mukattash TL, Shattat G, Al-Qirim T. Randomized controlled trial of clinical pharmacy management of patients with type 2 diabetes in an outpatient diabetes clinic in jordan. Journal of Managed Care Pharmacy. 2012;18(7):516–26.
Reason for exclusion: Not pharmacist prescribing

Kirking DM, Svinte MK, Berardi RR, Cornish LA, Chaffee BW, Ryan ML. Evaluation of direct pharmacist intervention on conversion from parenteral to oral histamine H2-receptor antagonist therapy. DICP - Annals of Pharmacotherapy. 1991;25(1):80–4.
Reason for exclusion: Not a controlled study – pre-test post-test

Kwan Y, Fernandes OA, Nagge JJ, Wong GG, Huh JH, Hurn DA, *et al*. Pharmacist Medication Assessments in a surgical preadmission clinic. Arch Intern Med. 2007;167:1034–40.

Reason for exclusion: Pharmacist transcribing, not prescribing. Pharmacist generates postoperative medication list. Surgeon then reviews list when patient is being discharged to indicate which medications are suitable for discharge

Lalonde L MJ Blais N, Montigny M, Ginsberg J, Fournier M, Berbiche D, Vanier MC, Blais L, Perreault S, Rodrigues I. Is long-term pharmacist-managed anticoagulation service efficient? A pragmatic randomized controlled trial. Am Heart J. 2008;156(1):148–54.
Reason for exclusion: Mixed hospital/community – control group was followed up at various places including hospital, physician's private office or community centers

Latter SB B, Smith A, Chapman ST M, Gerard K *et al.* Evaluation of nurse and pharmacist independent prescribing. 2010.
Reason for exclusion: Not a study

Latter S, Smith A, Blenkinsopp A, Nicholls P, Little P, Chapman S. Are nurse and pharmacist independent prescribers making clinically appropriate prescribing decisions? An analysis of consultations. Journal of health services research & policy. 2012;17(3):149–56.
Reason for exclusion: Compared nurse prescribing to pharmacist prescribing, mixed setting – hospital/community

Lee Y, Schommer JC. Effect of a pharmacist-managed anticoagulation clinic on warfarin-related hospital readmissions. Am J Health Syst Pharm. 1996;53:1580–3.
Reason for exclusion: Not considered pharmacist prescribing – did not specify that pharmacist prescribes warfarin doses

Mamdani MM, Racine E, McCreadie S, *et al.* Clinical and economic effectiveness of an inpatient anti-coagulation service. Pharmacotherapy. 1999;19(9):1064–74.
Reason for exclusion: Observational study

McFadzean E, Isles C, Moffat J, Norrie J, Stewart D. Is there a role for a prescribing pharmacist in preventing prescribing errors in a medical admission unit? Pharmaceutical Journal. 2003;270(7255): 896–9.
Reason for exclusion: Not a controlled study – pre-test post-test. Not considered pharmacist prescribing – pharmacist charted medication history for doctor to sign

McGhan WF, Stimmel GL, Hall TG, Gilman TM. A comparison of pharmacists and physicians on the quality of prescribing for ambulatory hypertensive patients. Medical Care. 1983;21(4):435–44.
Reason for exclusion: Not a controlled study – retrospective design

Mearns BM. Hypertension: Benefit of pharmacists prescribing antihypertensive medication. Nature Reviews Cardiology. 2015;12(8):443–443.
Reason for exclusion: Not a study – narrative only

Menard PJ, Krishner BS, Koth DD, Pyka RS, Hill LR, Ventakaraman K. Management of the hypertensive patient by the pharmacist prescriber. Hosp Pharm. 1986;21:20–33.
Reason for exclusion: Not a controlled study – pre-test post-test

Nelson LA, Cummings DM, Downs GE, Seaman JJ. Financial impact of a pharmacist-managed medication refill clinic. Military Medicine. 1984;149(5):254–6.
Reason for exclusion: Not a controlled study – pre-test post-test

Parekh R Ghee, C. Evaluation of a pharmacist controlled anticoagulation clinic. Br J Pharm Prac. 1987; 370–81.
Reason for exclusion: Not a controlled study – pre-test post-test

Patel-Naik B, Szeinbach SL, Seoane-Vazquez E, Snider MJ, Hevezi MS. Managing oral anticoagulation therapy by pharmacists in a specialty heart hospital. J Eval Clin Pract. 2010;16(1):192–5.
Reason for exclusion: Not a controlled study – pre-test post-test

Rapoport A, Akbik H. Pharmacist-managed pain clinic at a Veterans Affairs medical center. American Journal of Health-System Pharmacy. 2004;61(13):1341–3.
Reason for exclusion: Not a study – narrative only

Rosen CE, Holmes CE. Pharmacist's impact on chronic psychiatric outpatients in community mental health. Am J Hosp Pharm. 1978;35:704–8.
Reason for exclusion: Not hospital setting, study conducted at local community mental health centres

Saokaew S, Permsuwan U, Chaiyakunapruk N, Nathisuwan S, Sukonthasarn A. Effectiveness of pharmacist-participated warfarin therapy management: A systematic review and meta-analysis. Journal of Thrombosis and Haemostasis. 2010;8(11):2418–27.
Reason for exclusion: Did not specifically look at studies in the hospital setting

Schneider PJ, Larrimer JN, Visconti JA, Miller WA. Role effectiveness of a pharmacist in the maintenance of patients with hypertension and congestive heart failure. Contemp Pharm Pract. 1982;5(2):74–9.
Reason for exclusion: Not considered pharmacist prescribing Pharmacist makes suggestions in the study group. Doctor sees patient after pharmacist and makes amendments as necessary.

Scott J. Evaluation of the first pharmacist non medical prescriber in addiction treatment in Somerset: Report for Somerset DAAT. 2010.
Reason for exclusion: Not a study, no studies included

Shalansky KF, Sunderji R. A simple warfarin dosing nomogram for orthopedic prophylaxis. Canadian Journal of Hospital Pharmacy. 2000;53(1):4–44.
Reason for exclusion: Not a controlled study – pre-test post-test.

Stimmel GL, McGhan WF, Wincor MZ, Deandrea DM. Comparison of pharmacist and physician prescribing for psychiatric inpatients. American Journal of Hospital Pharmacy. 1982;39(9):1483–6.
Reason for exclusion: Study setting: health maintenance organization (HMO) mental health facility.

Willey ML, Chagan L, Sisca TS, Chapple KJ, Callahan AK, Crain JL, *et al.* A pharmacist-managed anticoagulation clinic: six year assessment of patient outcomes. Am J Health Syst Pharm. 2003;60:1033–7.
Reason for exclusion: Not a controlled study – observational, retrospective design

Williams S, Younis N. Impact of a pharmacist prescriber in a university hospital multidisciplinary diabetic clinic. Pharmacy World & Science. 2007;29(3):299–301.
Reason for exclusion: Not a controlled study – observational, retrospective design

Wong YM, Quek YN, Tay JC, Chadachan V, Lee HK. Efficacy and safety of a pharmacist-managed inpatient anticoagulation service for warfarin initiation and titration. Journal of Clinical Pharmacy and Therapeutics. 2011;36(5):585–91.
Reason for exclusion: Not pharmacist prescribing – pharmacist recommends dose only

You JHS, Cheng G, Chan TYK. Comparison of a clinical pharmacist–managed anticoagulation service with routine medical care: Impact on clinical outcomes and health care costs. Hong Kong Medical Journal. 2008;14:S23–7.
Reason for exclusion: Same study as the one by Chan 2006 which is already included in the review. Article by Chan also contains a satisfaction survey.

Appendix III: Characteristics of included studies

Study details	Inclusion & exclusion criteria	Intervention participant details	Control participant details	Outcome measures/study results	Author conclusions and reviewer's comments
Boddy[28] (2001) Medway Hospital (UK) Quasi experimental, prospectively controlled study 12 weeks	*Inclusion criteria:* Adult inpatients on medical wards prescribed warfarin therapy *Exclusion criteria:* Elderly care patients	*Dependent Prescribing (by protocol):* Doctors initiated warfarin prescribing according to guideline and pharmacist prescribed warfarin according to guidelines from Day 4 onwards N = 74 *Mean age:* 54 years (Range 17 – 74) *Gender:* Male: 36 (49%) Female: 38 (51%)	*Usual care:* Doctors initiated and continued prescribing warfarin according to guidelines N = 64 *Mean age:* 57 years (Range 23 – 74) *Gender:* Male: 34 (53%) Female: 30 (47%)	*Statistical methods:* χ2 test , Kruskal-Wallis **Percentage International Normalized Ratio (INR) (from Day 4 onwards):** - *Within target range:* Intervention: 58% Control: 18% p < 0.001 - *Subtherapeutic (INR < 2.0):* Intervention: 10% Control: 32% *Significance not reported* - *Supratherapeutic (INR > 6.0):* Intervention: 1% Control: 5% *Significance not reported*	**Author's conclusion:** The pharmacist demonstrated significantly better (p = 0.001) INR control compared to junior doctors in terms of INR being in therapeutic range from Day 4 onwards **Reviewer's comments:** Compared junior doctor prescribing to prescribing by a hematology pharmacist
Burns[29] (2004) Brighton General Hospital (UK) Quasi experimental, prospectively controlled study 11 months	*Inclusion criteria:* Elderly inpatients on medical wards prescribed warfarin therapy *Exclusion criteria:* Patients admitted with excess INR values where warfarin was not indicated in the short term	*Dependent Prescribing (by protocol):* Pharmacist prescribed warfarin according to guidelines following initiation of prescription by doctors (by writing "warfarin as per protocol" on chart) N = 33 *Mean age:* 81 years *Gender:* Not reported	*Usual care:* Doctors prescribed warfarin as usual and had access to warfarin prescribing guidelines N = 33 *Average:* 80 years *Gender:* Not reported	*Statistical methods:* Analysis of variance **Adverse events - warfarin related complications:** Intervention: 6% (2/33) – 2 strokes Control: 12% (4/33) – 1 stroke, 3 bleeds *Significance not reported* **Patients with:** - *Appropriate loading doses:* Intervention: 100% (14/14) Control: 73% (11/15) *Significance not reported;* *Fisher's exact test: p = 0.1* - *Appropriate maintenance doses following loading:* Intervention: 100% (14/14) Control: 46% (7/15) F (1, 26) = 17.33, p < 0.001 **Patients within target INR range:** - *Day 4 after loading:* Intervention: 57% (8/14) Control: 46% (7/15) *Significance not reported;* *Fisher's exact test: p = 0.72* - *On discharge/transfer:* Intervention: 68% (19/28) Control: 73% (22/30) *Significance not reported;* *Fisher's exact test: p = 0.77* - *At the outpatient clinic:* Intervention: 61% (13/21) Control: 79% (19/24) *Significance not reported;* *Fisher's exact test: p = 0.32* **Percentage patients under- or over- anticoagulated (+/− 0.2 INR units) at any point during treatment:** Intervention: 67% (22/33) Control: 91% (30/33) F (1, 64) = 6.17, p = 0.016	**Author's conclusion:** Warfarin-dosing by pharmacists for inpatients had a beneficial effect on most aspects of anticoagulation control **Reviewer's comments:** Compared three pharmacist prescribers with experience running an outpatient warfarin clinic with junior doctors

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Study details	**Inclusion & exclusion criteria**	**Intervention participant details**	**Control participant details**	**Outcome measures/study results**	**Author conclusions and reviewer's comments**
Chan et al.[21] (2006) Prince of Wales Hospital (Hong Kong) RCT 24 months	*Inclusion criteria*: Adult patients enrolled in an anticoagulation clinic who were newly commenced on warfarin with an anticipated treatment duration of 3 months or more and were able to provide written consent *Exclusion criteria*: Anticipated treatment duration with warfarin for less than 3 months	*Dependent Prescribing (by protocol)*: One clinical pharmacist prescribed warfarin according to guidelines N = 68 *Mean age +/− SD*: 58 years +/− 14 *Gender*: Male: 24 (35%) Female: 44 (65%)	*Usual care*: Physician run anticoagulation clinic managed by 2 hematologists who prescribed warfarin according to guidelines N = 69 *Mean age +/− SD*: 60 years +/− 14 *Gender*: Male: 38 (55%) Female: 31 (45%)	*Statistical methods*: Unpaired student's t-test, $\chi 2$ test, Fisher's exact test, Mann-Whitney test **Adverse events - warfarin-related complications (per 100 patient-years)** *Bleeding events*: - *Major*: Intervention: 1 (1.6) Control: 2 (3.1) p = 1.00 - *Fatal*: None in both groups *Significance not reported* *Thromboembolic events*: - *Major*: Intervention: 1 (1.6) Control: 1 (1.6) p = 1.00 - *Fatal*: None in both groups *Significance not reported* **Patient time spent**: - *In therapeutic INR range*: Intervention: 64% Control: 59% p < 0.001 - *In extended therapeutic range (+/− 0.2 INR units)*: Intervention: 78% Control: 76% p < 0.001 **Patient satisfaction survey (PSQ-18)** - Mean score: *General satisfaction*: Intervention: 4.0 +/− 0.5 Control: 3.8 +/− 0.5 p = 0.134	**Author's conclusion:** The pharmacist-managed anticoagulation service was more effective and less costly than the doctor-managed service in achieving target anticoagulation control for Chinese patients on warfarin therapy **Reviewer's comments:** All patients were Chinese. Study supported by the Health Care and Promotion Fund, Hong Kong
Chau et al.[34] (2006) Providence Hospital (Canada) Quasi experimental, controlled study 5 months	*Inclusion criteria*: Adult patients admitted for rehabilitation following orthopedic surgery, limb amputation or stroke and who were prescribed warfarin. *Exclusion criteria*: Admission lasted less than 24 hours, patients received less than 24 hours of warfarin therapy	*Dependent Prescribing (by protocol)*: A single certified anticoagulation pharmacist prescribed warfarin according to guidelines to patients who were admitted to a single rehabilitation unit and referred to the warfarin dosing service N = 33 *Mean age (range)*: 72 years (47 – 88) *Gender*: Male: 6 (18%) Female: 27 (82%)	*Usual care*: Warfarin dosing by rehabilitation physicians without the use of warfarin nomograms or anticoagulation training N = 33 *Mean age (range)*: 71 years (34–96) *Gender*: Male: 8 (24%) Female: 25 (76%)	*Statistical methods*: No statistical analysis performed **Adverse events – warfarin related complications:** - *New diagnosis of DVT, PE or CVA, or death related to warfarin therapy*: - *Deep Vein Thrombosis*: None in both groups - *Pulmonary Embolism*: Intervention: 0; Control: 1 (2%) - *Death*: Intervention: 0; Control: 1 (2%) - *Hemorrhagic events*: - *Minor*: Intervention: 1 (3%); Control: 2 (6%) - *Major*: Intervention: 0; Control: 2 (6%) - *Life-threatening*: None in both groups **Percentage INRs:** - *Within target range*: Intervention: 67.9%; Control: 50.9% - *Subtherapeutic (INR < 2.0)*: Intervention: 22.7%; Control: 33.2% - *Supratherapeutic (INR 3.01 – 3.99)*: Intervention: 9.1%; Control: 12.8% - *Supratherapeutic (INR 4 – 6)*: Intervention: 0.3%; Control: 2.1% - *Supratherapeutic (INR > 6.0)*: Intervention: 0%; Control: 0% **Mean time to first therapeutic INR:** Intervention: 2.8 days (Range 0 – 10) Control: 3 days (Range 0 – 14)	**Author's conclusion:** The warfarin dosing service was safer and more effective than dosing provided by doctors. The pilot project for pharmacy anticoagulation service was deemed successful and could be expanded to all rehabilitation units within the institution **Reviewer's comments:** The aim of this study was to implement and evaluate a warfarin dosing service for rehabilitation medicine. Patients in the control arm were managed by rehabilitation doctors and those in the intervention arm by a certified anticoagulation pharmacist. Patients in the concurrent control group were identified retrospectively and data obtained through chart reviews.

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Study details	Inclusion & exclusion criteria	Intervention participant details	Control participant details	Outcome measures/study results	Author conclusions and reviewer's comments
Chenella et al.[22] (1983) Los Angeles County-University of Southern California Medical Center (USA) RCT 5 months	Inclusion criteria: Adult inpatients requiring anticoagulation with heparin and warfarin. Exclusion criteria: Not specified	Dependent Prescribing (by protocol): Seven pharmacists prescribed heparin and warfarin doses according to guidelines to patients referred to the anticoagulant service. Doctors prescribed simulated doses (blinded) for study comparison N = 42 Mean age (+/− SD): 46 years +/− 16 Gender: Male: 19 (45%) Female: 23 (55%)	Usual care: One doctor prescribed heparin and warfarin doses. Pharmacist prescribed simulated doses (blinded) which was not administered. N = 39 Mean age (+/− SD): 52 years +/− 16 Gender: Male: 16 (41%) Female: 23 (59%)	Statistical methods: Unpaired student's t-test, χ2 analysis with Yate's correction **Adverse events (Hemorrhagic events):** - Minor: Intervention: 4 (10%) Control: 0 - Major: None in both groups Significance not reported **Time to reach therapeutic proconvertin and prothrombin:** Intervention: 5.7 +/− 1.4 days Control: 5.8 +/− 2.1 days Not statistically significant	Author's conclusion: Certified pharmacist prescribers can adjust anticoagulant doses for inpatients according to a protocol as safely as an experienced doctor Reviewer's comments: Both arms used a heparin protocol for dosage adjustment; warfarin dosage was adjusted using the proconvertin and prothrombin method. The doctor was new to the anticoagulation service while the pharmacists had a minimum of 6 months clinical experience treating patients with anticoagulants and were certified to prescribe.
Damaske and Baird[30] (2005) Baylor University Medical Centre (USA) Quasi experimental, controlled study 3 months	Inclusion criteria: Inpatients under the care of pulmonologists, vascular surgeons and two internal medicine hospitalist groups, who were prescribed warfarin Exclusion criteria: Patients with a prosthetic heart valve, target INR > 3, active bleeding, hematocrit < 25%, baseline INR > 1.3 without being on warfarin, epidural catheter, ventriculostomy or lumbar puncture within 24 hours	Dependent Prescribing (by protocol): Clinical pharmacists prescribed warfarin doses when the doctor wrote an order for "warfarin protocol per pharmacy". Warfarin was dosed according to guidelines but deviation from guideline allowed according to clinical judgement. N = 29 Age: Not reported Gender: Not reported	Usual care: Doctors prescribed warfarin doses using warfarin guidelines N = 22 Age: Not reported Gender: Not reported	Statistical methods: No statistical analysis performed **Adverse events – warfarin related complications:** Minor hemorrhagic events: Intervention: 2 (7%) Control: 3 (14%) No other adverse events, minor or major, occurred in either group **Patients receiving correct first dose of 5 mg:** Intervention: 29 (100%) Control: 15 (68%) Significance not reported Fisher's exact test: p = 0.2085 **Percentage patients with supratherapeutic INR:** Intervention: 5 (17%), INR range 3.3 – 7.4 Control: 6 (27%), INR range 3.4 – 6.2 Significance not reported **Average time to therapeutic INR:** Intervention: 6 days (Range 4 – 11) Control: 5.6 days (Range 4 – 11)	Author's conclusion: Pharmacist-managed inpatient warfarin protocol is an effective way of ensuring adherence to the latest evidence-based guidelines for warfarin administration. Reviewer's comments: First warfarin dose of 5 mg was deemed appropriate but it is unclear if this was based on existing local guidelines in the control group as doctors did not appear to have access to a protocol.

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Study details	Inclusion & exclusion criteria	Intervention participant details	Control participant details	Outcome measures/study results	Author conclusions and reviewer's comments
Hale et al.[19] (2013) Princess Alexandra Hospital (Australia) RCT 4 months	*Inclusion criteria*: Adult patients scheduled for elective surgery and attending preadmission clinic and able to provide written consent. *Exclusion criteria*: Patients under 18 years of age, unable to communicate due to language difficulties, undergoing day surgery. Renal transplant and urology patients excluded from venous thromboembolism prophylaxis	*Supplementary prescribing*: Patients seen by a nurse, prescribing pharmacist, RMO and anesthetist. Patients were seen by the pharmacist before the RMO to enable counter-signature of prescriptions which was a site requirement. Pharmacist undertook all pharmacist duties as per usual care, as well as prescribing medications on the chart, including continuing or withholding medications and prescribing venous thromboembolism prophylaxis. N = 194 *Mean Age*: 55.8 years (Range 18 – 86) *Gender*: Male: 114 (59%) Female: 80 (41%)	*Usual care*: Patients seen by a nurse, pharmacist, resident medical officer (RMO) and anesthetist in no particular order. The RMO prescribed medications on the medication chart. N = 190 *Mean age*: 57.6 years (Range 18–89) *Gender*: Male: 110 (58%) Female: 80 (42%)	*Statistical methods*: χ2 test, Fisher's exact test, logistic regression **Accuracy of medication charts:** - *Unintentional medication omissions (not prescribed)*: Intervention: Total 11/887 (1.2%), Regular medications: 3 (0.3%), PRN medications: 8 (0.9%) Control: Total 383/1217 (31.5%), Regular medications: 248 (20.4%), PRN medications: 135 (11.1%) p < 0.001 for regular medications - *Prescribing errors*: Intervention: 2 (0.2%) Control: 51 (6.3%) p < 0.001 - *Number of pharmacist prescriptions which required modification by a doctor*: 5 minor changes, 3 addition of analgesics out of the pharmacist's prescribing scope, 2 changes resulted in inappropriate VTE prophylaxis **Appropriate prescribing of chemical or mechanical venous thromboembolism prophylaxis:** - *In preadmission clinic*: Intervention: 93.8% Control: 63.9% p < 0.001 - *On admission*: Intervention: 93.1% Control: 89.5% p = 0.29	**Author's conclusion:** Medication charts in the intervention arm contained fewer clinically significant omissions and prescribing errors, when compared with controls. There was no difference in appropriateness of VTE prophylaxis on admission between the two groups. **Reviewer's comments:** The pharmacist prescriber had a postgraduate diploma in clinical pharmacy, 3 years of experience in hospital pharmacy and had attended a prescribing course which was accredited in the UK. Clinical significance of omissions is reported in Hale et al.[20] (below)
Hale et al.[20] (2014) Princess Alexandra Hospital (Australia) RCT 4 months	As in Hale et al.[19]	*Supplementary prescribing*: As in Hale et al. (2013) N = 10 *Mean Age*: 58 years (Range 34 – 77) *Gender*: Male: 6 (60%) Female: 4 (40%)	*Usual care*: As in Hale et al.[19] N = 9 *Mean age*: 73 years (Range 55 – 85) *Gender*: Male: 6 (67%) Female: 3(33%)	*Statistical methods*: χ2 test, Fisher's exact test **Appropriateness of prescriptions:** (According to a modified Medication Appropriateness Index; Outcomes were assessed by a panel consisting of a consultant anesthetist, a consultant hepatobiliary surgeon, a consultant clinical pharmacologist, a senior pharmacist, a senior nurse and a resident medical officer) *Inappropriate prescriptions*: *Overall (combined assessment)*: Intervention: 13/266 (4.9%) Control: 32/294 (10.9%) Significance not reported; Fisher's exact test: p = 0.0121 *Based on individual reviewer's assessment*: Only statistically significant for the pharmacist with no medications assessed as inappropriate in the intervention arm compared to 6/61 medications in the control arm (p = 0.029). *Unintentional medication omissions (regular medications)*: Intervention: 1/55 (2%) Control: 25/89 (28%) p < 0.001 *Clinical significance of medication omissions*: Intervention: Only 1 reviewer thought the single occurrence of omission was significant Control: On average, 52% omissions rated to have potential to cause patent harm or ward inconvenience	**Author's conclusion:** Appropriateness of prescribing was similar between arms, Medication charts in the control arm contained slightly more omissions than the intervention arm, a number of which were rated by the panel members as having the potential for patient harm or inconvenience **Reviewer's comments:** In this paper, 5% of the patient population from Hale et al.[19] (2013) were randomly selected, and is a part of a larger study.

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Study details	Inclusion & exclusion criteria	Intervention participant details	Control participant details	Outcome measures/study results	Author conclusions and reviewer's comments
Hawkins et al.[23] (1979) Robert B Green Hospital (USA) RCT 29 months	Inclusion criteria: All adult patients with hypertension and diabetes seen at the medical follow up clinic Exclusion criteria: Patients dismissed due to absence of chronic illness, incomplete medical record, enrolled in another study, transferred to another health care facility, late entry into the study	Collaborative prescribing: Pharmacist with 2 years of clinical training in general medicine managed patients, assisted by doctor of pharmacy candidates. All patient-care assessments and plans made by the pharmacist were subsequently reviewed by doctor auditors to assure provision of adequate medical care to patients N = 349 Mean Age: 61 years Gender: Male: 85 (24.4%) Female: 264 (75.6%)	Usual care: Clinical physician (Assoc. Prof. of family practice) assisted by 4 vocational nurses provided usual care. N = 280 Mean age: 60 years Gender: Male: 63 (22.5%) Female: 217 (77.5%)	Statistical methods: $\chi 2$ analysis with Yate's correction, z test, t-test, analysis of covariance **Pre-trial and post-trial SBP, DBP, fasting BSLs:** Mean Systolic Blood Pressure (mm Hg): - Pre-trial: Intervention: 145 +/− 15 Control: 143 +/− 14 Not statistically significant - Post-trial (between 24 to 29 months): Intervention: 147 +/− 18 Control: 141 +/− 13 $p \leq 0.001$, t = 3.88 Mean Diastolic Blood Pressure (mm Hg): - Pre-trial: Intervention: 86 +/− 6 Control: 86 +/− 6 Not statistically significant - Post-trial (between 24 to 29 months): Intervention: 84 +/− 6 Control: 84 +/− 4 Not statistically significant Mean fasting Blood Sugar Level (mg/dL): - Pre-trial: Intervention: 192 +/− 46 Control: 182 +/− 39 $p \leq 0.05$ - Post-trial (between 24 to 29 months): Intervention: 184 +/− 42 Control: 189 +/− 49 p = 0.058	**Author's conclusion:** This study provides additional evidence to justify safe and effective role of the clinical pharmacist in the post-diagnostic management of patients with diabetes mellitus and hypertension. Most patients were Mexican Americans
Jacobs et al.[24] (2012) Lahey Hospital and Medical Centre (USA) RCT 12 months	Inclusion criteria: Adult patients with Type 2 diabetes seen in an ambulatory general medicine clinic, over 18 years old, HbA1c > 8% which was obtained more than 6 months before data acquisition date, able to provide consent Exclusion criteria: Patients who received primary care outside of Lahey Clinic Burlington campus, diagnosis of Type 1 diabetes, HbA1c < 8% within 6 months of randomization, enrolled in other pharmacist-run or diabetes management study, receiving diabetes management by an outside endocrinologist, unable to adhere to scheduled follow-up	Supplementary Prescribing: 5 pharmacist practitioners with a minimum of postgraduate residency training with emphasis in ambulatory care and experience in directly caring for patients with chronic diseases managed the care of patients. Their duties included adjustment in therapy, lab testing or referral to other services, which required approval by the referring physician before being implemented by the pharmacist. N = 72 Mean age (+/− SD): 62.7 years +/− 10.8 Gender: Male: 49 (68%) Female: 23 (32%)	Usual care: Physicians provided usual care N = 92 Mean age +/− SD: 63.0 years +/−11.2 Gender: Male: 51 (55%) Female: 41 (45%)	Statistical methods: Unpaired t tests, Fisher's exact tests **Pre-trial and post-trial HbA1c, LDL cholesterol, SBP, DBP:** Mean HbA1c +/− SD (%): - Pre-trial: p = 0.07 Intervention: 9.5 +/− 1.1 Control: 9.2 +/− 1.0 - Post-trial (12 months): p = 0.003 Intervention: 7.7 +/−1.3 Control: 8.4 +/− 1.6 Mean LDL +/− SD (mmol/L): - Pre-trial: p = 0.227 Intervention: 3.1 +/− 0.8 Control: 3.0 +/− 0.9 - Post-trial (12 months): p = 0.01 Intervention: 2.4 +/− 0.5 Control: 2.7 +/− 0.9 Mean SBP +/− SD (mm Hg): - Pre-trial: p = 0.003 Intervention: 142.5 +/− 15.2 Control: 134.8 +/− 16.9 - Post-trial (12 months): p = 0.223 Intervention: 132.5 +/− 16.3 Control: 135.4 +/− 14 Mean DBP +/− SD (mm Hg): - Pre-trial: p = 0.493 Intervention: 79.4 +/− 9.9 Control: 78.3 +/− 10.4 - Post-trial (12 months): p = 0.001 Intervention: 72.0 +/− 8.5 Control: 77.6 +/− 8.4 **Patients reaching primary endpoints for HbA1c ($\leq$7%) , LDL cholesterol ($\leq$100 mg/dL), SBP ($\leq$ 130 mm Hg), DBP ($\leq$ 80 mm Hg):** No statistically significant differences between arms	**Author's conclusion:** For all indices measured, this study demonstrated that collaborative diabetes management with a clinical pharmacist can improve overall care **Reviewer's comments:** This study received an unrestricted medical grant from Pfizer

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Study details	Inclusion & exclusion criteria	Intervention participant details	Control participant details	Outcome measures/study results	Author conclusions and reviewer's comments
Marotti et al.[25] (2011) John Hunter Hospital (Australia) RCT Study duration not specified	*Inclusion criteria*: Adult elective surgery patients admitted on the day of surgery *Exclusion criteria*: Orthopedic surgery patients, no regular medications, unable to provide consent, medication charted during pre-operative clinic visit, admitted as day-only patient	*Supplementary Prescribing*: Pharmacist interviewed patients on day of surgery and documented a regular medication list, which was also prescribed on the medication chart. Pharmacist prescribing was guided by protocols which advised which medications should be withheld and for how long depending on type of surgery N = 118 *Median age (IQR)*: 64 years (47 – 75) *Gender*: Male: 60 (51%) Female: 58 (49%)	*Usual care*: Patients had their medications charted immediately prior to surgery or postoperatively by a doctor in the normal time-frame. No clinical pharmacist consultations occurred prior to surgery N = 118 *Median age (IQR)*: 65 years (54 – 75) *Gender*: Male: 58 (49%) Female: 60 (51%)	*Statistical methods*: Not specified **Average number doses missed inappropriately during inpatient stay**: Intervention: 1.07 (CI 0.9 – 1.25) Control: 3.21 (CI 2.89 – 3.52) $p = 0.002$ **Average number medications charted at incorrect dose (CI)**: Intervention: 0.02 (95% CI 0 – 0.04) Control: 0.48 (95% CI 0.35 – 0.61) $p < 0.05$ **Average number medications charted at incorrect frequency (CI)**: Intervention: 0.015 (CI 0 – 0.06) Control: 0.29 (CI 0.19 – 0.39) $p < 0.05$	**Author's conclusion**: Many patients miss doses of regular medication during their hospital stay and preoperative medication history taking and supplementary prescribing by a pharmacist can reduce this. **Reviewer's comments**: In the control group, patients' regular medications were obtained post discharge by the trial pharmacist over the phone.
Pawloski and Kersh[31] (1992) St Joseph's Hospital (USA) Quasi experimental, prospectively controlled study 6 months – two phases	*Inclusion criteria*: Inpatients commenced on treatment with continuous heparin *Exclusion criteria*: Patients treated with thrombolytic agents (e.g. streptokinase), patients who were treated with heparin for less than 24 hours	*Dependent Prescribing (by protocol)*: Doctors wrote an order for "heparin per protocol" to initiate pharmacist prescribing. Doctors could also initiate prescribing before electing to have the patient managed by the pharmacist. Once initiated, pharmacists calculated the loading dose and initial infusion rate based on patient weight and current diagnosis. Following this, any changes were managed according to protocol. **Phase I**: N = 29 *Age*: Not reported *Gender*: Not reported **Phase II**: N = 31 *Age*: Not reported *Gender*: Not reported	*Usual care*: Consultant doctors provided usual care – use of the heparin protocol was not mandatory **Phase I**: N = 14 *Age*: Not reported *Gender*: Not reported **Phase II**: N = 14 *Age*: Not reported *Gender*: Not reported	*Statistical methods*: Not specified **Number of days of heparin therapy per patient (Mean +/– SD)**: -Phase I: Intervention: 4.66 +/– 2.54 Control: 5.43 +/– 2.29 *Not statistically significant* -Phase II: Intervention: 4.39 +/– 2.09 Control: 4.79 +/– 2.01 *Not statistically significant* **Time to reach therapeutic APTT (Mean +/– SD)**: -Phase I: Intervention: 16.52 +/– 10.92 Control: 46.5 hours +/– 34.13 $p < 0.001$ -Phase II: Intervention: 9.32 +/– 3.78 Control: 31.64 +/– 32.74 $p < 0.001$	**Author's conclusion**: When voluntarily prescribed by doctors, full-dose continuous intravenous heparin therapy initiated and monitored by clinical pharmacists improved the quality of patient's anticoagulation treatment during hospitalization. **Reviewer's comments**: The aim of this study was to implement a new heparin protocol and compare doctor and pharmacist prescribing. The study was carried out in 2 phases – the second phase was carried out following revision of the heparin protocol to a lower therapeutic APTT range (from 55–80 seconds) to 45–75 seconds)
Schillig et al.[32] (2011) Henry Ford Hospital (USA) Quasi experimental, prospectively controlled study 19 months	*Inclusion criteria*: Adult inpatients on 2 internal medicine and 2 cardiology wards who received at least one inpatient dose of warfarin *Exclusion criteria*: Patients not scheduled for follow-up in the Henry Ford Medical Group outpatient anticoagulation clinics after discharge	*Prescribing model unclear*: Five anticoagulation pharmacists who had several years of general-medicine based clinical practice experience or residency training, or both, were responsible for initial dose selection and daily dose adjustment after warfarin was initiated by the primary team. N = 250 *Mean age +/– SD*: 64.1 years +/– 15.6 *Gender*: Male: 135 (54%) Female: 115 (46%)	*Usual care*: Patients' management of anticoagulation at discretion of the primary care team. The primary care team had access to a clinical pharmacist who was not part of the Pharmacist-Directed Anticoagulation Service (PDAS) N = 250 *Mean age +/– SD*: 68 years +/– 14.9 *Gender*: Male: 141 (56.4%) Female: 109 (43.6%)	*Statistical methods*: Student's t test, Mann-Whitney U test, χ^2, Fishers exact test **Adverse events – warfarin related complications (during hospitalization or within 30 days of discharge)**: - *Major bleeding events (%)*: Intervention: 2 (0.8%) Control: 1 (0.4%) $p = 0.563$ - No thromboembolic events in either group **Number of episodes of INR > 5 during hospitalization or within 30 days of discharge**: Intervention: 24 (9.6%) Control: 37 (14.8%) $p = 0.076$	**Author's conclusion**: Implementation of a pharmacist directed anticoagulation service provides a net improvement in quality of care for the patient taking warfarin in the inpatient setting **Reviewer's comments**: It is unclear if the physicians or pharmacists had access to a warfarin dosing nomogram.

	Study details	Inclusion & exclusion criteria	Intervention participant details	Control participant details	Outcome measures/study results	Author conclusions and reviewer's comments
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	Tong et al.[33] (2016) The Alfred Hospital (Australia) Quasi experimental, prospectively controlled study 19 weeks	*Inclusion criteria*: Adult patients admitted to general medical units and emergency short-stay units (ESSU) with complex medication regimens or polypharmacy from 7am to 9pm, 7 days a week. *Exclusion criteria*: Medication chart written by doctor before pharmacist review or patient admitted to ESSU and not reviewed by a pharmacist	*Supplementary Prescribing*: A credentialed pharmacist (at least 2 years of experience in hospital pharmacy and 6 months experience in general medicine and credentialed to prescribe) took a medication history, performed a VTE risk assessment, and had a face to face discussion with the admitting doctor about current medical and medication-related problems, following which a medication management plan was agreed upon. Appropriate pre-admission medications and VTE prophylaxis were charted by the pharmacist. N = 408 *Age*: 75 years *Gender*: Male: 175 (42.9%) Female: 233 (57.1%)	*Usual care*: Standard medication charting by doctors of relevant teams, with subsequent medication reconciliation performed by a pharmacist within 24 hours of admission N = 473 *Age*: 71.5 years *Gender*: Male: 218 (46.1%) Female: 255 (53.9%)	*Statistical methods*: χ2, Fishers exact test, Student's t test, Wilcoxon rank-sum test **Patients with medication errors detected within 24 hours of admission** (omitted drug, incorrect dose/frequency, incorrect/unnecessary drug, incorrect route): Intervention: 15/408 (3.7%) Control: 372/473 (78.7%) p < 0.001 **Severity of errors per patient**: p < 0.01 -*Low risk*: Intervention: 0 Control: 13 (2.7%) -*Moderate risk*: Intervention: 4 (1%) Control: 81 (17.1%) -*High risk*: Intervention: 1 (0.2%) Control: 150 (31.7%) -*Extreme risk*: Intervention: 0 Control: 25 (5.3%) NNT to prevent a case of high risk or extreme error: 2.7 patients **Error type**: p < 0.01 -*Omitted drug (not prescribed)*: Intervention: 12; Control: 1397 -*Incorrect dose*: Intervention: 7; Control: 138 -*Incorrect frequency*: Intervention: 0; Control: 5 -*Incorrect/unnecessary drug*: Intervention: 0; Control: 33	**Author's conclusion**: Partnering between medical staff and pharmacists to jointly chart initial medications on admission significantly reduced inpatient medication errors (including errors of high and extreme risk) among general medical and emergency short-stay patients with complex medication regimens or polypharmacy. **Reviewer's comments**: Errors were identified by an independent pharmacist assessor who was not blinded to randomization. Errors were then reviewed and assigned a risk rating by a blinded independent expert panel comprising of a general doctor, an emergency doctor and a senior clinical pharmacist. Study was funded by the Department of Health and Human Services, Victoria
	Vivian[26] (2002) Veteran Affairs Medical Centre (VAMC), Philadelphia (USA) RCT 6 months	*Inclusion criteria*: Over 18 years, essential hypertension on anti-hypertensive therapy, BP > 140/90, receiving all medications from VAMC pharmacy, not receiving existing care from pharmacy-managed clinic, signed informed consent forms *Exclusion criteria*: Secondary cause of hypertension, missed more than 3 appointments in the last year, hypertensive crisis, NYHA class III or IV heart failure, end stage renal disease, psychiatric disorder, severe hepatic dysfunction, terminal cancer, other condition that limited life expectancy to 1 year	*Dependent Prescribing (by protocol)*: Patients scheduled once a month at the hypertension clinic to see pharmacist who had prescribing authority to make appropriate drug therapy changes in both drug selection and dosage in accordance with the sixth report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure N = 26 *Mean Age +/− SD*: 64 +/− 10.9 *Gender*: Male: 26 (100%)	*Usual care*: Patients received traditional pharmacy services but did not make monthly visits to the pharmacist-managed hypertension clinic N = 27 *Mean age +/− SD*: 65.5 years +/− 7.8 *Gender*: Male: 27 (100%)	*Statistical methods*: Paired t test, two-sample t test, Fishers exact test, Wilcoxon rank-sum test **Pre-trial and post-trial SBP and DBP**: *Mean SBP +/− SD (mm Hg)*: - *Pre-trial*: Intervention: 149.0 +/− 15.3 Control: 152.8 +/− 14.3 p = 0.252 - *Post-trial (6 months)*: Intervention: 130.5 +/− 13.2 Control: 148.4 +/− 21 p = 0.0002 *Mean DBP +/− SD (mm Hg)*: - *Pre-trial*: Intervention: 89.8 +/− 10.9 Control: 77.9 +/− 11.9 p = 0.0012 - *Post-trial (6 months)*: Intervention: 77.5 +/− 10.7 Control: 80.4 +/− 11.4 p = 0.259 **Patients achieving target Blood Pressure**: (< 140/90 mm Hg or < 130/80 mm Hg in diabetics) Intervention: 21 (81%) Control: 8 (30%) p = 0.001 **Patient satisfaction survey**: Number of patients who experience the following situation most of the time (Data for sometimes, very rarely and never not shown): "I am very satisfied with the pharmacy services that I receive" Intervention: 88% Control: 68% p = 0.098	**Author's conclusion**: Pharmaceutical care improves blood pressure control and results in more patients with hypertension reaching their blood pressure goal. **Reviewer's comments**: Most patients were African Americans

(Continued)

Study details	Inclusion & exclusion criteria	Intervention participant details	Control participant details	Outcome measures/study results	Author conclusions and reviewer's comments
Weeks and Fyfe[27] (2012) Barwon Health (Australia) RCT 6 months	*Inclusion criteria*: Adult patients with peripheral vascular disease attending a vascular outpatient clinic, provided consent, had a LDL cholesterol level of at least 2 mmol/L *Exclusion criteria*: Minors, pregnant, unable to provide consent, part of another compliance study, unwilling or not able to be followed up for a 6 month period, poorly controlled diabetes (HbA1c >7%), dyslipidemia requiring medical intervention, contraindication or hypersensitivity to lipid lowering drugs	*Collaborative Prescribing*: Patients reviewed by a pharmacist with 7 years clinical experience during four 6-weekly visits. At each visit patients were given lifestyle advice. Before starting on a statin, they were provided with information and if patients agreed, statin was prescribed at the following visit. A statin dose adjustment and monitoring algorithm was available as a guide if required. N = 8 *Mean Age +/− SD*: 73 years +/− 9.5 *Gender*: Male: 5 (62.5%) Female: 3 (37.5%)	*Usual care*: Patients were given dietary advice, a booklet on cholesterol management and their lipid levels measured at baseline and 6 months. N = 6 *Mean age +/− SD*: 79 years +/− 6.1 *Gender*: Male: 3 (50%) Female: 3 (50%)	*Statistical methods*: No statistical analysis - sample size too small **Pre-trial and post-trial LDL and total cholesterol:** *Mean Low Density Lipoprotein (mmol/L)*: - *Pre-trial*: Intervention: 2.9 Control: 3.1 - *Post-trial (6 months)*: Intervention: 1.8 Control: 3.1 *Mean total cholesterol (mmol/L)*: - *Pre-trial*: Intervention: 5.2 Control: 5.3 - *Post-trial (6 months)*: Intervention: 4.0 Control: 5.1	**Author's conclusion:** A suitably trained hospital pharmacist can undertake extended roles with a prescribing element. **Reviewer's comments:** The study failed to recruit the target of 31 patients in each arm due to difficulties with recruitment and follow-up. All prescriptions written by the pharmacist were countersigned by a cardiologist to meet statutory requirements.