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Pharmacist-led Chronic Disease Management: A Systematic Review of Effectiveness and Harms Compared to Usual Care

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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TABLE OF CONTENTS

TABLES

FIGURES

EXECUTIVE SUMMARY

INTRODUCTION

Increased involvement of clinical pharmacists in patient care may offer increased access to health care and improved patient outcomes. Defined by Hepler and Strand in 1989, pharmaceutical care involves pharmacist collaboration with health team members to optimize therapeutic outcomes by identifying, solving, and preventing actual and potential drug therapy problems. Since 1995, the Department of Veterans Affairs has allowed Clinical Pharmacy Specialists (CPS) an expanded scope of practice with independent prescribing privileges. In this capacity, CPS have been detailed to perform "pharmaceutical care" or comprehensive medication management along with chronic disease state management services, in addition to less complex services such as patient medication counseling or responding to drug information questions. In the VA primary care setting, CPS are likely to be responsible for therapeutic outcomes for a multitude of conditions for any patient referred to CPS or proactively identified by CPS as a high-risk patient.

The purpose of this review is to determine the effectiveness and harms of pharmacist-led chronic disease management for community-dwelling adults. Chronic disease management aims to control symptoms and slow or stop disease progression. Chronic disease management is typically a multi-component intervention that includes medication therapy review, patient medication education, medication monitoring, immunizations, disease self-care and support, and/or prescribing authority.

This topic was nominated by Heather Ourth, PharmD, VACO Pharmacy Benefits Management Program Manager, on behalf of the National Clinical Pharmacy Research Group, chartered by the VACO Clinical Pharmacy Practice Office of VACO Pharmacy Benefits Management (PBM). We address the following key question developed with input from the topic nominator and a technical expert panel (TEP).

Key Question: What are the effectiveness and harms of pharmacist-led chronic disease management compared to usual care?

Population: Adults (age 18 or older)
Interventions: Chronic disease management; pharmacist takes responsibility for some component of the management or prevention of one or more chronic diseases (*eg*, chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF], diabetes, hypertension, cancer, chronic kidney disease [CKD], pain, depression) (*ie*, pharmacist-led care)
Comparator: Usual care without the services provided by the pharmacists to the intervention group
Outcomes:

- *Clinical Outcomes (including intermediate clinical measures):* disease-specific clinical events (*ie,* severe hypoglycemia or hypotension requiring additional interventions), depression, mortality, health related quality of life, patient satisfaction, disease specific intermediate goal attainment such as glycated hemoglobin [HbA1c], blood pressure, and lipid levels
- *Resource Use*: office visits, urgent care or emergency room visits, hospitalizations, access to care, and costs

• *Medications:* appropriate medications and dosages, drug interactions, (non)adherence, other

Timing: No minimum follow-up required

Setting: Interventions that take place within the United States and are provided to outpatients by pharmacists based in healthcare facilities

METHODS

Data Sources and Searches

We searched MEDLINE (Ovid), CINAHL, the Cochrane Library, and the International Pharmaceutical Abstracts (IPA) database for articles published from 1995 through June 2015. We obtained additional articles by hand-searching the reference lists of systematic reviews and included studies and we also received reference suggestions from peer reviewers.

Study Selection

Abstracts from MEDLINE were independently reviewed in duplicate by investigators and research associates. All other abstracts were reviewed by a single co-investigator or research associate. We included studies of any design that reported on the effectiveness or harms of pharmacist-led chronic disease management in adult outpatients with, or at risk for, a chronic disease. We excluded studies that did not test an intervention that was pharmacist-led (*ie*, where the pharmacist was responsible for a component of patient care), studies without a comparator, studies that did not take place in a healthcare facility in the US (*eg,* studies set in retail pharmacies), and studies of anticoagulation clinics because pharmacist management is considered standard care.

Full-text reports of studies identified as potentially eligible based on abstract review were obtained for further review. Each article was independently reviewed by 2 investigators or research associates.

Data Abstraction and Risk of Bias Assessment

Study characteristics (target population, inclusion/exclusion criteria, intervention goal, follow-up duration, primary outcomes, pharmacist type, setting, and intervention and comparator descriptions) and outcomes (primary and secondary outcomes reported in the studies and broadly categorized as clinical, resource use, and medications) were extracted into evidence tables by one investigator or research associate and verified by another. We assessed the risk of bias based on the following criteria: allocation of subjects to comparison groups, allocation concealment, risk of bias from confounding (for non-randomized studies), blinding, completeness of outcome reports including losses to follow-up, and selective outcome reporting – a modification of the Cochrane approach to determining risk of bias.

Data Synthesis and Analysis

We organized evidence tables by disease state of the study population. We described and qualitatively summarized the characteristics and findings of included studies. Outcomes data were pooled where possible. However, pooled analyses were not appropriate for many outcomes due to heterogeneity of interventions and outcome reporting.

We rated the overall strength of the body of evidence across chronic disease conditions for disease-specific clinical events, patient satisfaction, target goal attainment, urgent care/emergency department visits and hospitalizations, and medication adherence using the method reported by Owens et al.

RESULTS

Results of Literature Search

We reviewed 1,342 abstracts, 504 from MEDLINE and the remaining from additional databases. We excluded 1,151 abstracts and reviewed the full text of 191 articles. During full-text review we excluded 134 articles leaving 57 eligible for inclusion. Hand-searching reference lists of pertinent trials and systematic reviews and peer reviewer suggestions identified an additional 13 references.

We included 70 papers representing 62 studies with 64 unique study populations (k) in cardiovascular diseases (k=6), chronic kidney disease (k=4), chronic obstructive pulmonary disease (k=1), depression (k=4), diabetes mellitus (k=24), dyslipidemia (k=7), hypertension (k=15), and polypharmacy/high risk (k=3). An overview of study characteristics is presented in Executive Summary Table 1.

Summary of Results

Overall findings: (Executive Summary Tables 1-3)

- Most studied interventions included pharmacist-led medication monitoring, medication therapy review, prescribing authority, and/or disease self-care and support.
- Interventions were typically delivered by pharmacists in-person and over multiple times. However, interventions varied in composition, delivery mode, and intensity, making it difficult to draw conclusions about important intervention characteristics.
- Studies were generally short-term and designed to assess intermediate outcomes such as blood pressure, cholesterol, and/or glucose goal attainment in patients with diabetes, hypertension, or cardiovascular disease rather than other clinical or resource use outcomes.
- Many of the outcomes reported in this review were not primary study endpoints supported by rigorous research methods or statistical inferences. Findings based on analyses of outcomes other than the study-defined primary outcomes should be interpreted with caution.
- Most trials reporting disease-specific clinical events found pharmacist-led care and usual care to be similar. However, only 3 of the included studies were designed to assess clinical events, outcomes were sporadically and inconsistently reported, and there were few events (low strength of evidence). Eight studies reported mortality with all finding similar mortality in the pharmacist-led care and control groups.
- Compared to usual care, pharmacist-led care was associated with similar incidences or rates of office, urgent care or emergency department visits, and hospitalizations (moderate strength of evidence) and medication adherence (low strength of evidence).

- There was insufficient evidence to evaluate the effect of pharmacist-led care on patient satisfaction. There was limited reporting of quality of life outcomes.
- No studies reported typical measures of access to care (*eg,* wait time for appointment or percentage of appointments within a specified window of a desired appointment time). Four studies reported either patient satisfaction with reaching someone in an emergency or availability of advice about health condition (both significantly higher in the intervention group) or patient perceptions of communication with the care team and problems getting care (intervention and control groups similar).
- There was limited reporting of harms or other drug-related problems (defined for this review as inappropriate medication or dosage and drug interactions). Studies that reported harms often did not provide data for the control group participants.
- Reported cost outcomes included total costs, medication costs, cost savings per patient, and program costs, but few studies found significant differences between intervention and control groups.
- Patients in the pharmacist-led care groups generally received a greater number or dose of medications although it was difficult to evaluate whether increased number or dose of medications was an indicator of better care quality.
- Compared to usual care, pharmacist-led care improved study-selected glycemic, blood pressure, and lipid goal attainment (moderate strength of evidence).

Executive Summary Table 1. Summary of Included Studies

Characteristic	(Risk of) Cardio-vascular Disease	Chronic Kidney Disease	Chronic Obstructive Pulmonary Disease	Depression	Diabetes Mellitus	Dyslipidemia	Hypertension	Polypharmacy/ High Risk	Total
Total									
Studies	6	4	1	4	24	7	15	3	**64[a]**
Total Patients	3,403	2,920	98	926	17,716	1,834	6,278	1,282	**34,457**
Design									
RCT	4	2	1	3	12	2	13	3	**40**
Other	2	2	0	1	12	5	2	0	**24**
Setting									
VA	1	2	1	0	4	4	4	1	**17**
Non-VA	5	2	0	4	20	3	11	2	**47**
Intervention									
Medication Monitoring	6	4	1	3	22	6	14	2	**58**
Medication Therapy Review	2	2	0	3	13	3	10	2	**35**
Patient Medication Education	2	0	0	3	9	3	4	2	**23**
Prescribing Authority	3	2	0	3	12	5	7	1	**33**
Disease Self-care and Support	4	2	1	4	22	3	14	2	**52**
Immunizations	0	0	0	0	2	0	0	0	**2**
Delivery Mode									
Remote	1	0	0	1	2	2	1	0	**7**
In-Person	4	3	0	0	14	4	8	2	**35**
Mixed	1	1	1	3	8	1	6	1	**22**
Intervention Frequency									
One-time	2	0	0	0	4	1	0	0	**7**
Multiple	4	4	1	4	20	6	15	3	**57**
Risk of Bias									
Low	1	1	0	1	5	0	2	1	**11**
Medium	3	3	1	2	15	3	12	2	**41**
High	2	0	0	1	4	4	1	0	**12**

RCT = randomized controlled trial; VA = Veterans Affairs

[a] 2 studies reported separate results for 2 different disease conditions

Executive Summary Table 2. Number of Studies Reporting Each Outcome (and Study-Defined Primary Outcome)[a]

Condition (number of included studies)	Clinical						Resource Use					Medication					
	Clinical Events	Depression	All-Cause Mortality	Health-Related Quality of Life	Patient Satisfaction	Goal Attainment	Office Visits	Urgent Care/Emergency Room Visits	Hospitalizations	Access to Care[b]	Costs	Inappropriate Dosage/ Prescription	Ineffectiveness	Drug Interactions	(Non)-adherence	Number/Dose of Appropriate Medications	Other
Cardiovascular Diseases (k=6)	2		2 (1)	1	1	3 (2)	2	3 (1)	5 (1)		2	1			3 (1)	3	
Chronic Kidney Disease (k=4)	2		2	1	1	3 (1)			1		3	1			1	4	
Chronic Obstructive Pulmonary Disease (k=1)				1	1		1 (1)	1 (1)	1 (1)			1		1		1	
Depression (k=4)		2 (2)		3	4 (1)		3 (1)	2		2	1				3 (2)	3 (1)	
Diabetes (k=24)	4		3	3	3	16 (10)	6	8 (1)	8 (1)	1	3	1			4	15	4
Dyslipidemia (k=7)						7 (3)	4	1			2				1	6	
Hypertension (k=15)	6		1	7 (2)	7 (1)	13 (8)	9	3	4	1	4 (1)	2		1	11 (1)	13	
Polypharmacy/ High-risk (k=3)	1			2 (2)	2 (1)	2 (1)	1	1 (1)	2 (1)		2	1 (1)	1	1	2 (2)	3	
TOTAL (64 unique study populations)[c]	**15**	**2 (2)**	**8 (1)**	**18 (4)**	**19 (3)**	**44 (25)**	**26 (2)**	**19 (4)**	**21 (4)**	**4**	**17 (1)**	**7 (1)**	**1**	**3**	**25 (6)**	**48 (1)**	**4**

[a] some studies didn't have one of our outcomes as their primary outcome and some had more than one primary outcome; table entries are number of studies reporting that outcome as their primary outcome

[b] access to care assessed as patient satisfaction (reaching someone in an emergency, availability of advice) or patient perceptions (communication with the care team and problems getting care)

[c] 2 studies reported separate results for 2 different disease conditions

Executive Summary Table 3. Strength of Evidence[a]

Outcome	Strength of Evidence	Direction	Number of RCTs (N)	Summary
Disease-specific clinical events[b]	Low	Similar	12 (3,355)	Most trials found similar outcomes between pharmacist-led care and usual care. Outcomes were sporadically and inconsistently reported and there were few events. Overall risk of bias was moderate.
Patient satisfaction	Insufficient	Mixed	16 (12,793)	Results were inconsistent for measures of patient satisfaction between pharmacist-led care and usual care. There was variation in how patient satisfaction was reported (scale score or proportions), some measures may not be validated, and some trials used a single item from a multi-item scale. Overall risk of bias was moderate. Given these limitations, conclusions regarding the strength of evidence for patient satisfaction cannot be determined.
Urgent care/ER and hospitalizations	Moderate	Similar	Urgent care/ER 16 (7,166) Hospitalizations 12 (7,455)	Incidence or rates of urgent care/ER visits or hospitalizations were similar between pharmacist-led care and usual care. Overall risk of bias was moderate.
Non-adherence to medications	Low	Similar	17 (5,933)	In most trials medication non-adherence was similar between pharmacist-led care and usual care. Overall risk of bias was moderate. Pooled results from 7 (n=1479) demonstrated a substantial relative reduction but findings were imprecise, not significant, and had substantial heterogeneity (RR 0.58 [95% CI 0.33, 1.01]; I^2 = 82%).
Goal attainment	Moderate	Improved in pharmacist-led care groups	19 (5,816)	Pharmacist-led care improved the proportion of patients achieving guideline- recommended laboratory or physiologic treatment goals versus usual care, 51% vs 34% (RR 1.56 [95% CI 1.37, 1.78]; I^2 = 48%). Results were precise and fairly consistent. Cluster RCTs, CCTs, and cohort studies not included in the pooled analysis generally reported improved goal attainment in the pharmacist-led care group. Overall risk of bias was moderate.

[a] Strength of evidence determined for specific outcomes across all chronic disease conditions
[b] *ie,* severe hypoglycemia or hypotension requiring additional interventions

Condition-specific Findings

Cardiovascular Disease or Risk Factors (4 RCTs, 2 Cohort Studies)

- Pharmacist-led care
  - resulted in mortality and rates of disease-specific clinical events that were similar to usual care; only one study reported a clinical event as a primary outcome,
  - was associated with mixed results for maintenance or attainment of HbA1c and blood pressure goals compared to usual care,
  - resulted in hospitalization rates that were similar to usual care; there were mixed results for office visits, urgent care visits, and costs; only one study reported resource use as a primary outcome, and
  - was associated with mixed results for medication use and adherence as compared to usual care.
- No studies reported on access to care, or drug interactions or other drug-related problems.

Chronic Kidney Disease (2 RCTs, 2 Cohort Studies)

- Pharmacist-led care
  - improved kidney disease-related quality of life at one year but not 2 years among patients at a university-affiliated dialysis center but resulted in similar quality of life for Veterans with CKD in primary care.
  - lowered medication use in the intervention group in the dialysis study,
  - increased use of anti-hypertensive medications in the VA study with intervention and control groups similar on blood pressure goal attainment,
  - resulted in similar all-cause mortality between groups in both studies, and
  - to manage anemia due to CKD was associated with a lower weekly dose of EPO (k=1), more medication adjustments if hemoglobin levels were low (but not high) (k=1), cost savings (k=2), and better attainment of target hemoglobin (k=2) and iron saturation values (k=1) versus usual care; intervention and control sites reported similar rates of adverse events (k=1).
- No studies reported on office or emergency department visits, access to care, or drug interactions or other drug-related problems.

Chronic Obstructive Pulmonary Disease (1 RCT)

- Multifaceted pharmacist-led care from 8 VA Medical centers
  - resulted in health-related quality of life, number of new medications, number of emergency department visits, and a rate of hospitalization that were similar to usual care,
  - decreased office visits, and
  - resulted in mixed findings for patient satisfaction (*ie,* significant differences on some subscales).
- Effects on drug-related problems were reported only for the intervention group.
- All-cause mortality, disease-specific clinical events, access to care, and costs were not reported.

Depression (3 RCTs, 1 non-RCT)

- Pharmacist-led care
  - was similar to usual care for depressive symptoms and health-related quality of life,
  - was similar to usual care for medication adherence (2 RCTs reporting); self-reported use of antidepressant medications and changes in antidepressant medications were more frequent in the pharmacist-led care groups,
  - resulted in numbers/rates of primary care or urgent care visits that were similar to usual care, and
  - increased patient satisfaction with availability of advice.
- All-cause mortality, hospitalizations, costs, inappropriate prescriptions, drug interactions and other drug-related problems and harms were not compared.

Diabetes (12 RCTs, 2 CCTs, 10 Cohort Studies)

- Pharmacist-led care
  - resulted in all-cause mortality, disease-specific clinical events, and health-related quality of life that was similar to usual care, although few studies reported these outcomes,
  - improved rates of goal attainment for HbA1c, blood pressure, and lipids; the 3 studies in VA settings reported increased attainment of HbA1c and blood pressure goals in patients receiving pharmacist-led care,
  - resulted in significantly higher numbers and/or doses of medications, and
  - resulted in resource use (office visits, urgent care or emergency department visits, and hospitalizations) that was similar to usual care.
- One study reported access to care favoring the intervention group; no studies reported drug interactions or other drug-related problems.

Dyslipidemia (2 RCTs, 2 CCTs, 3 Cohort Studies)

- Pharmacist-led care
  - improved goal attainment (typically LDL < 100 mg/dL) compared to usual care although pooled results from 2 RCTs showed groups were similar,
  - was associated with increased medication use; one study reported adherence in the intervention group but not the usual care group, and
  - led to mixed results for office visits and similar results for urgent care or emergency department visits and costs as usual care.
- No studies reported other clinical outcomes (*ie,* mortality, disease-specific clinical events, health-related quality of life, and patient satisfaction), hospitalizations, access to care, inappropriate prescriptions, or drug interactions or other drug-related problems.

Hypertension (13 RCTs, 1 CCT, 1 Case-Control Study)

- Pharmacist-led care
  - resulted in similar health-related quality of life as usual care; patient satisfaction results were mixed and few studies reported other clinical outcomes,
  - increased medication use but adherence was similar to usual care,

  - led to mixed results for resource use outcomes including office visits and costs; few studies reported urgent care or emergency room visits, and
  - resulted in patient perceptions similar to usual care for "had problems getting needed care."
- No studies reported drug interactions or other drug-related problems; one study reported inappropriate medications for the intervention group but not the control group.

Polypharmacy/High Risk for Drug-related Problems (3 RCTs)

- Pharmacist-led care
  - resulted in health-related quality of life; patient satisfaction, and rates/numbers of disease-specific clinical events that were similar to usual care; goal attainment was improved,
  - resulted in similar medication use as usual care; results were mixed for medication adherence; significance of other medication findings could not be determined, and
  - increased the number of office visits compared to usual care but decreased use of urgent care facilities; results were mixed for hospitalizations and costs.
- No studies reported all-cause mortality or access to care.

DISCUSSION

Summary of Findings and Strength of Evidence

We rated strength of evidence for disease-specific clinical events (low strength of evidence that pharmacist-led care and usual care were similar), patient satisfaction (insufficient evidence), urgent care/emergency department visits and hospitalizations (moderate strength of evidence that pharmacist-led care and usual care were similar), non-adherence to medications (low strength of evidence that pharmacist-led care and usual care were similar), and goal attainment (moderate strength of evidence that pharmacist-led care increased the proportion of patients achieving glycemic, blood pressure, and cholesterol goals compared to usual care). While we did not formally assess strength of evidence on other outcomes we did find that pharmacist-led care was also similar to usual care for depression, health-related quality of life, all-cause mortality, and cost outcomes. However, due to differences in costs reported across studies (program costs, medication costs, visit costs), it is difficult to reach a conclusion about costs. Very few studies reported drug-related problems (inappropriate medication or dosage, drug interactions). Patients in the pharmacist-led care groups generally received a greater number or dose of medications although it was difficult to evaluate whether increased number or dose of medications was an indicator of better care quality.

Applicability

The chronic disease conditions addressed in the included studies (cardiovascular disease, chronic kidney disease, COPD, depression, diabetes mellitus, and hypertension) are common among Veterans. Seventeen studies were conducted in VA facilities. The model of pharmacist-led care reported in these studies varied but likely is similar to ongoing programs in VA.

Limitations/Research Gaps/Future Research

Many of the outcomes reported in this review were not the study-defined primary endpoints and therefore were not supported by rigorous research methods or statistical inferences. Among studies included in our review, sample sizes were too small and follow-up periods too short to detect differences in mortality. There was limited reporting of other clinical events, health-related quality of life, and patient satisfaction. When assessed, authors used varied methods for determining health-related quality of life and patient satisfaction. Scale scores were often not validated, of unknown clinical importance, or included selected findings from subscales. Interventions varied in composition, delivery mode, and intensity as did the usual care comparator, making it difficult to draw conclusions about important intervention characteristics.

One hypothetical benefit of pharmacist-led care for chronic diseases is increased access to care for patients. None of the included studies reported typical measures of access and only 4 studies (2 in patients with depression and one each in patients with hypertension or diabetes) reported patient satisfaction or patient perception measures related to access (*eg,* satisfaction with ability to reach someone in an emergency or satisfaction with availability of advice). Intervention-based increases in the number of scheduled visits or telephone calls may not represent improved access. Further research is needed with conventional measures of access.

A consistent definition of an office visits outcome is needed to distinguish regularly scheduled office visits, study-related office visits, and unplanned office visits. In many cases it was unclear whether the visit was with a pharmacist or primary care provider. Also, a consistently reported cost outcome that includes all of the important economic factors involved in pharmacist-led care would facilitate comparisons across studies and provide more accurate cost-effectiveness estimates.

There was limited reporting of important drug-related problems, in particular drug interactions and inappropriate medications and/or dosages. Some studies did report on adherence with mixed, inconclusive results. Despite existing definitions of polypharmacy, an isolated measure of the number of medications is not an indicator of quality of care as there are situations where adding medications and/or increasing dosages may be helpful. Similarly, de-prescribing medications that emerging evidence suggests are not beneficial and may provide harm may also be helpful. Further research is needed to define and describe these interventions and their association with patient outcomes and value.

Finally, the demonstrated improvement in laboratory and physiologic goal attainment due to pharmacist-led care is potentially encouraging. Intervention group pharmacists successfully achieved the intended study objectives. The target goals were based, in part, on recommendations from selected existing clinical practice guidelines and performance measures. The results indicate that future pharmacist-led programs are likely to achieve intended goals. However, there is conflicting evidence that target goals for glycemic, blood pressure, or cholesterol control have long-term beneficial effects on patient outcomes including clinical events, satisfaction, access, hospitalizations, and costs. Therefore, future research needs to carefully assess whether the magnitude of effect on selected intermediate laboratory and physiologic goals translate to improved patient outcomes including clinical events, satisfaction, access, hospitalizations, and costs. Few studies reported differences in potential harms. Thus the available evidence does not answer the question about whether the benefits of pharmacy-led

interventions justify potential harms and costs. Ideally, future studies will be designed to fully and accurately address final patient outcomes and cost effectiveness.

Conclusions

Evidence is limited on the effectiveness and harms of pharmacist-led chronic disease management compared to usual care for clinical outcomes (*ie,* clinical events, all-cause mortality, patient satisfaction, quality of life, and resource utilization). Moderate-strength evidence indicates that pharmacist-led chronic disease management increases goal attainment for HbA1c, blood pressure, and cholesterol levels. Moderate- or low-strength evidence also indicates that pharmacist-led chronic disease management and usual care were similar for urgent care visits or hospitalizations, clinical events, and adherence to medications. Evidence was insufficient for patient satisfaction. There was little reporting of access to care and drug-related problems. These results suggest that future programs are likely to achieve intended laboratory and physiologic goals. However, to accurately assess health care value, future research studies and implementation projects that utilize intermediate laboratory and physiologic goals as measures of effectiveness need to be certain that these goals are clearly linked to improved patient outcomes including clinical events, satisfaction, access, hospitalizations, costs, medication adherence, and drug-related problems without undue harms and costs.

ABBREVIATIONS TABLE

BP	Blood pressure
CCT	Controlled clinical trial (non-randomized)
CPS	Clinical Pharmacy Specialist
HbA1c	Hemoglobin A1c
HTN	Hypertension
HDL, HDL-C	High density lipoprotein cholesterol
LDL, LDL-C	Low density lipoprotein cholesterol
MTM	Medication Therapy Management
PharmD	Doctor of Pharmacy
RCT	Randomized controlled clinical trial
RR	Risk ratio
VA	Veterans Affairs

EVIDENCE REPORT

INTRODUCTION

Increased involvement of clinical pharmacists in patient care may offer increased access to primary care services and improved health care for patients.[1,2] Recently introduced bills H.R. 592 and S. 314, the Pharmacy and Medically Underserved Areas Enhancement Act, are aimed to improve patient access to health care through pharmacists' patient care services. The bills would help officially establish pharmacists as health care providers and enable coverage of pharmacists' services through Medicare Part B in medically underserved communities.

Furthermore, pharmacist involvement in patient care may help to reduce inappropriate medication use, specifically in the elderly. A study in 2007 revealed that more than 85% of Veterans over the age of 65 who received care in VA outpatient facilities were given a potentially inappropriate medication.[3] Inappropriate prescriptions cost the United States billions of dollars in healthcare expenditures annually and can result in increased morbidity, adverse drug events, hospitalization, and mortality.[4,5] A study in Canada saw the proportion of patients receiving an inappropriate medication drop significantly after medication review and optimization by a team that included a pharmacist.[6]

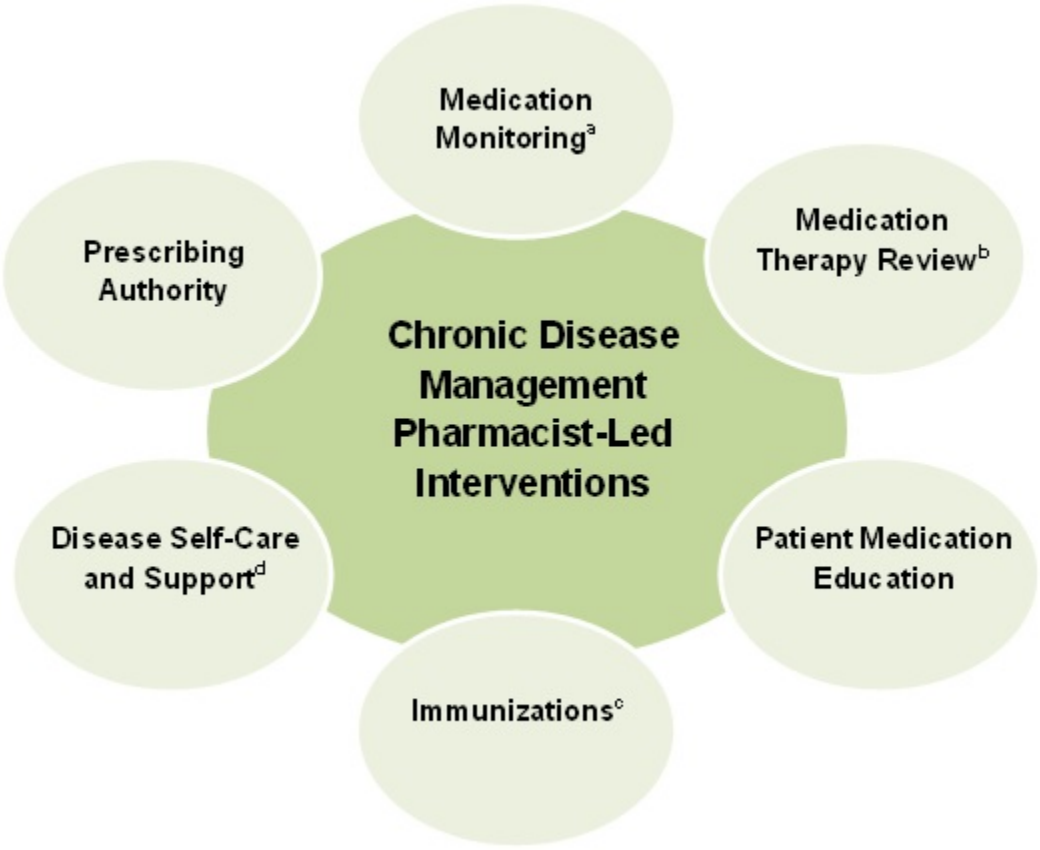
Hepler and Strand defined pharmaceutical care as pharmacist collaboration with health team members to optimize therapeutic outcomes by identifying, solving, and preventing actual and potential drug therapy problems.[7] Since 1995, the Department of Veterans Affairs has allowed Clinical Pharmacy Specialists (CPS) an expanded scope of practice with independent prescribing privileges.[8] In this capacity, CPS have been detailed to perform "pharmaceutical care" or comprehensive medication management along with disease state management services in addition to less complex services such as patient medication counseling or responding to drug information questions. In the VA primary care setting, CPS are likely to be responsible for therapeutic outcomes for a multitude of conditions for any patient referred to CPS or proactively identified by CPS as a high-risk patient.

A 2014 systematic review of outpatient medication therapy management (MTM) interventions addressed 5 areas: 1) intervention components and features, 2) effectiveness in comparison to usual care, 3) factors under which outpatient-based MTM is effective and optimally delivered, 4) types of patients likely to benefit, and 5) types of patients at risk of harms from such programs.[9] The review did not address MTM services provided by pharmacists shortly after hospital discharge, independent disease management services, or single episode contact. Interventions needed, at minimum, 3 elements to satisfy the inclusion criteria for the systematic review: comprehensive medication review, patient-directed education and counseling, and coordination of care, including prescriber-directed interventions. The MTM intervention criteria for the review were broader than the Medicare Part D MTM-defined interventions. Outpatient settings included long-term care settings, pharmacy call centers, and retail pharmacies. The review included interventions conducted in non-U.S. countries but published in English. Evidence was insufficient for many patient-centered outcomes of interest; however, MTM interventions improved medication appropriateness, adherence, and percentage of patients achieving a threshold adherence level while medication dosing was reduced. For some patient conditions,

MTM interventions were associated with lowered odds of hospitalization and lower hospitalization costs. There was no observed benefit of MTM for patient satisfaction.

The purpose of this review is to identify the effectiveness and harms of pharmacist-led chronic disease management for community-dwelling adults with chronic diseases. Chronic disease management is a type of care that can be provided by pharmacists and aims to control symptoms and slow or stop disease progression. Chronic disease management is a multi-component intervention. We categorized intervention components as medication monitoring, medication therapy review, patient medication education, immunizations, disease self-care and support, and/or prescribing authority as detailed in Figure 1.

Figure 1. Components of Pharmacist-Led Chronic Disease Management



[a] Medication Monitoring: follow-up after prescription for medication effectiveness and safety, drug-related problems
[b] Medication Therapy Review: includes medication reconciliation
[c] Immunizations: pharmacist provides immunization; immunization was not an outcome of interest
[d] Disease Self-care and Support: facilitate access to other health care professionals; education about disease, lifestyle changes; aspirin therapy; tobacco cessation

SCOPE OF REVIEW

This review focused on chronic disease management for outpatients in health care facilities excluding retail pharmacies. We emphasized patient- or health system-centered outcomes but also addressed intermediate measures including achievement of recommended therapeutic goals. Due to differences in pharmacy practices in other countries, this review was limited to U.S. studies.

We address the following key question developed with input from the topic nominator and a technical expert panel (TEP). The scope of the review is also depicted in an analytic framework (Figure 2).

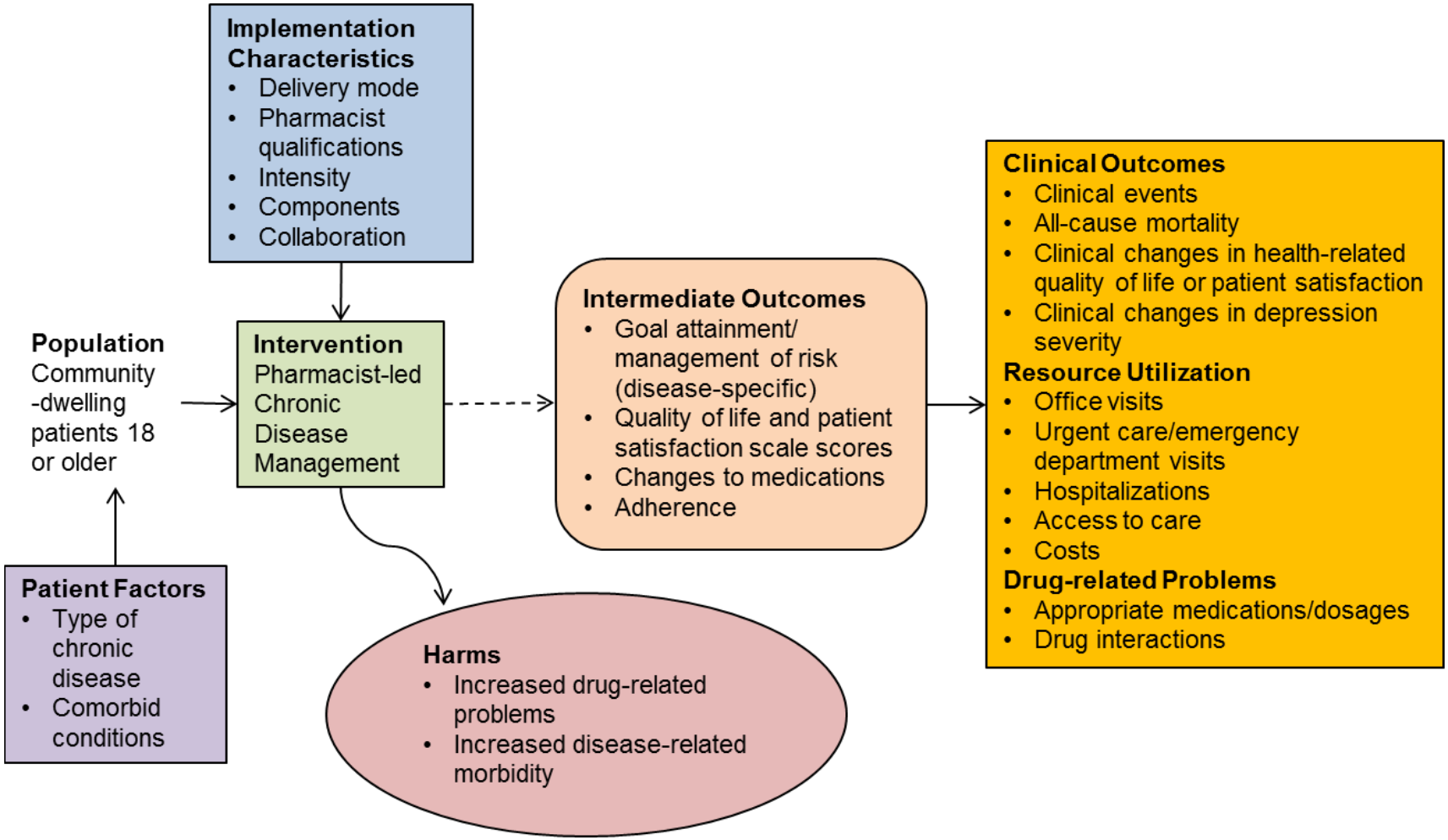
Key Question: What are the effectiveness and harms of pharmacist-led chronic disease management compared to usual care?

Population: Adults (age 18 or older)
Interventions: Chronic disease management; pharmacist takes responsibility for some component of the management or prevention of one or more chronic diseases (*eg*, chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF], diabetes, hypertension, cancer, chronic kidney disease [CKD], pain, depression) (*ie*, pharmacist-led care)
Comparator: Usual care without the services provided by the pharmacists to the intervention group
Outcomes:

- *Clinical Outcomes (including intermediate clinical measures):* disease specific clinical events (*ie,* severe hypoglycemia or hypotension requiring additional interventions), depression, mortality, health related quality of life, patient satisfaction, disease specific intermediate goal attainment such as glycated hemoglobin [HbA1c], blood pressure, and lipid levels
- *Resource Use*: office visits, urgent care or emergency room visits, hospitalizations, access to care, and costs
- *Medications:* appropriate medications and dosages, drug interactions, (non)adherence, other

Timing: No minimum follow-up required
Setting: Interventions that take place within the United States and are provided to outpatients by pharmacists based in healthcare facilities

Figure 2. Analytic Framework



METHODS

TOPIC DEVELOPMENT

This topic was nominated by Heather Ourth, PharmD, VACO Pharmacy Benefits Management Program Manager, on behalf of the National Clinical Pharmacy Research Group, chartered by the VACO Clinical Pharmacy Practice Office of VACO Pharmacy Benefits Management (PBM). The evidence review examines the effectiveness (both clinical and economic) of pharmacist-led chronic disease management compared to usual care.

SEARCH STRATEGY

We searched MEDLINE (Ovid), CINAHL, the Cochrane Library, and the International Pharmaceutical Abstracts (IPA) database for articles published from 1995 through June 2015. Our search was designed to identify studies that included control groups and was limited to studies enrolling adults and published in the English language. The search included the MeSH terms pharmacists, disease management, patient care, case management, patient education as topic, medication therapy management, drug interactions, drug therapy, drug monitoring, medication reconciliation, and patient care management. The full search strategies are presented in Appendix A. We obtained additional articles by hand-searching the reference lists of systematic reviews and other reports and from peer reviewer suggested references.

STUDY SELECTION

Abstracts from MEDLINE (n=504) were independently reviewed in duplicate by investigators and research associates. Abstracts from the CINAHL database (n=5 unique to CINAHL), IPA (n=588), and Cochrane (n=245) were reviewed by a co-investigator or research associate. We included studies of any design (including quality improvement projects) reporting on the effectiveness or harms of pharmacist-led care in outpatient adults with, or at risk for developing, a chronic disease. We excluded the following:

- Studies that did not include outpatient adults with or at risk for a chronic disease,
- Studies that did not test an intervention that was pharmacist-led, where the pharmacist was responsible for a component of patient care and, if part of a collaborative care team, the contribution of the pharmacist could be distinguished from other team members
- Studies that did not involve interventions intended to manage or prevent one or more chronic disease(s),
- Studies without a comparator,
- Studies that did not take place in a healthcare facility in the US (*eg*, studies set in retail pharmacies), and
- Studies of anticoagulation clinics because pharmacist management is considered standard care.

Full-text reports of studies identified as potentially eligible were obtained for further review using the inclusion and exclusion criteria described above. Each article was independently reviewed by 2 investigators or research associates. Reasons for excluding a study at full text review were noted.

DATA ABSTRACTION

Study characteristics (target population, inclusion/exclusion criteria, goal of intervention, primary outcome, duration/follow-up of study, type of pharmacist, study setting, intervention and comparator descriptions, and collaboration) as well as study-reported primary and secondary outcomes (drug-related problems, mortality, quality of life, access, patient satisfaction, healthcare utilization, cost, and goal attainment) were extracted onto evidence tables by one investigator or research associate and verified by another.

RISK OF BIAS ASSESSMENT

We assessed the risk of bias based on the following criteria: sequence generation, allocation concealment, risk of bias from confounding (for non-randomized studies), blinding, incomplete outcome reporting, and selective outcome reporting – a modification of the Cochrane approach to determining risk of bias. (Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Intervention Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.) Individual studies were rated as low, medium, or high risk of bias. Low risk of bias RCTs had adequate allocation concealment, blinding, and outcome reporting. Low risk of bias non-randomized studies also had low risk of bias from confounding.

DATA SYNTHESIS

We organized evidence tables by disease state of the study population. We described and qualitatively compared the characteristics and findings of included studies. If pooling was feasible, data were analyzed in RevMan 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). Random effects models (DerSimonian-Laird) were used to calculate pooled risk ratios (RR) with 95% confidence intervals (CI) for categorical outcomes. However, pooled analyses were not possible for many outcomes due to heterogeneity of interventions and outcome reporting across studies. Therefore, most findings are summarized in narrative form.

RATING THE BODY OF EVIDENCE

We rated the overall strength of the body of evidence for clinical events, patient satisfaction, target goal attainment, urgent care/emergency department visits and hospitalizations, and medication adherence using the method reported by Owens et al.[10]

PEER REVIEW

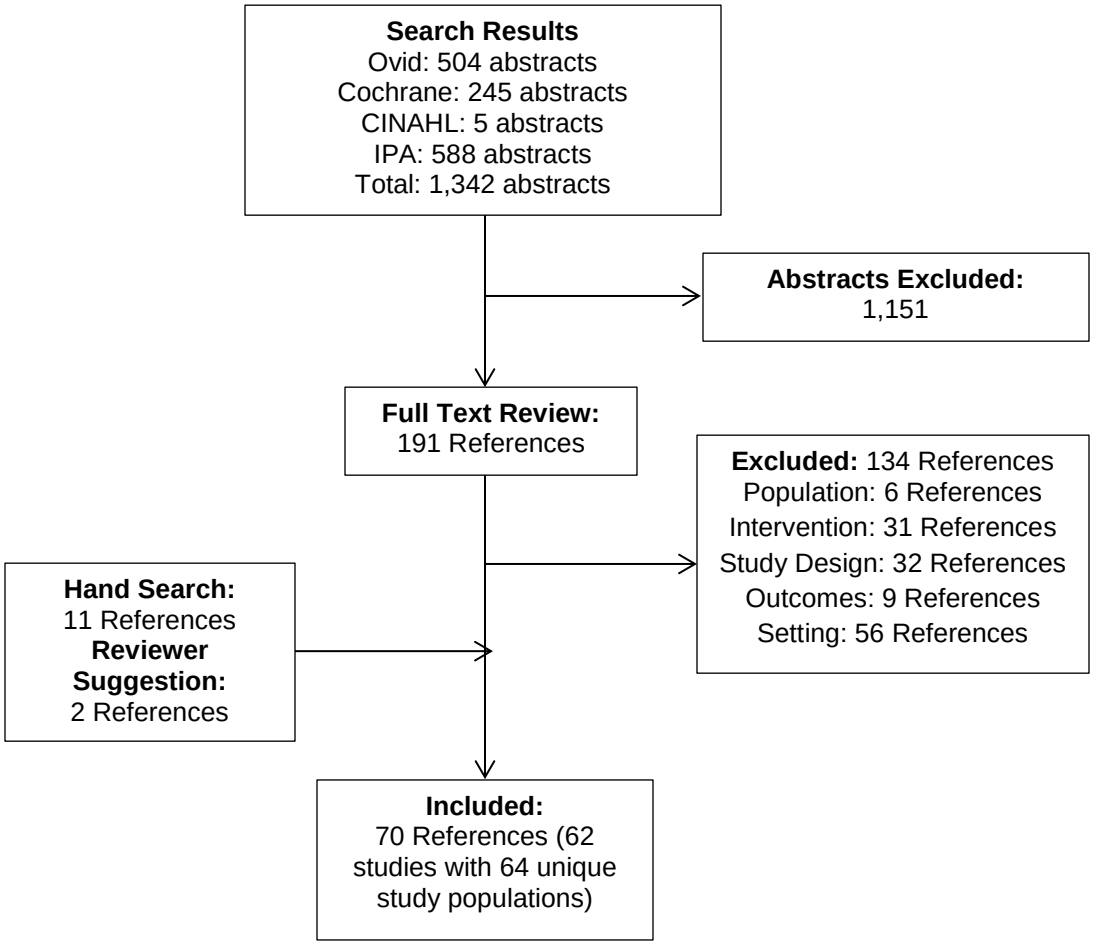
A draft version of this report was reviewed by content experts as well as clinical leadership. Reviewer's comments and our responses are presented in Appendix B and the report has been modified as needed.

RESULTS

LITERATURE FLOW

We reviewed 1,342 abstracts, 504 from MEDLINE, 588 from IPA, and the remaining from Cochrane and CINAHL. We excluded 1,151 abstracts and reviewed the full text of 191 references. During full-text review we excluded 134 articles leaving 57 eligible for inclusion. Hand-searching pertinent trials and systematic reviews identified an additional 11 references. Two additional references were suggested by a peer reviewer. Figure 3 details the process.

Figure 3. Literature Flow Chart



OVERVIEW OF INCLUDED STUDIES

We included 70 papers representing 62 studies with 64 unique study populations (k) in cardiovascular diseases (k=6), chronic kidney disease (k=4), chronic obstructive pulmonary disease (k=1), depression (k=4), diabetes mellitus (k=24), dyslipidemia (k=7), hypertension (k=15), and polypharmacy/high risk (k=3). Characteristics of the included studies are summarized in Table 1.

Table 1. Summary of Included Studies

Characteristic	(Risk of) Cardio-vascular Disease	Chronic Kidney Disease	Chronic Obstructive Pulmonary Disease	Depression	Diabetes Mellitus	Dyslipidemia	Hypertension	Polypharmacy/ High Risk	Total
Total									
Studies	6	4	1	4	24	7	15	3	**64[a]**
Total Patients	3,403	2,920	98	926	17,716	1,834	6,278	1,282	**34,457**
Design									
RCT	4	2	1	3	12	2	13	3	**40**
Other	2	2	0	1	12	5	2	0	**24**
Setting									
VA	1	2	1	0	4	4	4	1	**17**
Non-VA	5	2	0	4	20	3	11	2	**47**
Intervention									
Medication Monitoring	6	4	1	3	22	6	14	2	**58**
Medication Therapy Review	2	2	0	3	13	3	10	2	**35**
Patient Medication Education	2	0	0	3	9	3	4	2	**23**
Prescribing Authority	3	2	0	3	12	5	7	1	**33**
Disease Self-Care and Support	4	2	1	4	22	3	14	2	**52**
Immunizations	0	0	0	0	2	0	0	0	**2**
Delivery Mode									
Remote	1	0	0	1	2	2	1	0	**7**
In-Person	4	3	0	0	14	4	8	2	**35**
Mixed	1	1	1	3	8	1	6	1	**22**
Intervention Frequency									
One-time	2	0	0	0	4	1	0	0	**7**
Multiple	4	4	1	4	20	6	15	3	**57**
Risk of Bias									
Low	1	1	0	1	5	0	2	1	**11**
Medium	3	3	1	2	15	3	12	2	**41**
High	2	0	0	1	4	4	1	0	**12**

RCT = randomized controlled trial; VA = Veterans Affairs

[a] 2 studies reported separate results for 2 different disease conditions

Table 2 depicts all outcomes of interest reported in the studies (with study-defined primary outcomes in parentheses). Goal attainment (*ie,* reaching target goals for HbA1c, blood pressure, and/or cholesterol levels) was the primary outcome for 25 of the 64 unique population studies. Few studies identified other clinical, resource use, or medication outcomes as their primary outcome.

Table 2. Number of Studies Reporting Each Outcome (and Study-defined Primary Outcome)[a]

Condition (number of included studies)	Clinical						Resource Use					Medication					
	Clinical Events	Depression	All-Cause Mortality	Health-Related Quality of Life	Patient Satisfaction	Goal Attainment	Office Visits	Urgent Care/Emergency Room Visits	Hospitalizations	Access to Care[b]	Costs	Inappropriate Dosage/ Prescription	Ineffectiveness	Drug Interactions	(Non)-adherence	Number/Dose of Appropriate Medications	Other
Cardiovascular Diseases (k=6)	2		2 (1)	1	1	3 (2)	2	3 (1)	5 (1)		2	1			3 (1)	3	
Chronic Kidney Disease (k=4)	2		2	1	1	3 (1)			1		3	1			1	4	
Chronic Obstructive Pulmonary Disease (k=1)				1	1		1 (1)	1 (1)	1 (1)			1		1		1	
Depression (k=4)		2 (2)		3	4 (1)		3 (1)	2		2	1				3 (2)	3 (1)	
Diabetes (k=24)	4		3	3	3	16 (10)	6	8 (1)	8 (1)	1	3	1			4	15	4
Dyslipidemia (k=7)						7 (3)	4	1			2				1	6	
Hypertension (k=15)	6		1	7 (2)	7 (1)	13 (8)	9	3	4	1	4 (1)	2		1	11 (1)	13	
Polypharmacy/ High-risk (k=3)	1			2 (2)	2 (1)	2 (1)	1	1 (1)	2 (1)		2	1 (1)	1	1	2 (2)	3	
TOTAL (64 unique study populations)[c]	**15**	**2 (2)**	**8 (1)**	**18 (4)**	**19 (3)**	**44 (25)**	**26 (2)**	**19 (4)**	**21 (4)**	**4**	**17 (1)**	**7 (1)**	**1**	**3**	**25 (6)**	**48 (1)**	**4**

[a] some studies didn't have one of our outcomes as their primary outcome and some had more than one primary outcome; table entries are number of studies reporting that outcome as their primary outcome

[b] access to care assessed as patient satisfaction (reaching someone in an emergency, availability of advice) or patient perceptions (communication with the care team and problems getting care)

[c] 2 studies reported separate results for 2 different disease conditions

KEY QUESTION: WHAT ARE THE EFFECTIVENESS AND HARMS OF PHARMACIST-LED CHRONIC DISEASE MANAGEMENT COMPARED TO USUAL CARE?

Cardiovascular Disease (4 RCTs, 2 Cohort Studies)

Key Findings

- Pharmacist-led care
  - resulted in mortality and rates of disease-specific clinical events that were similar to usual care; only one study reported a clinical event as a primary outcome,
  - was associated with mixed results for maintenance or attainment of HbA1c and blood pressure goals compared to usual care,
  - resulted in hospitalization rates that were similar to usual care; there were mixed results for office visits, urgent care visits, and costs; only one study reported resource use as a primary outcome, and
  - was associated with mixed results for medication use and adherence as compared to usual care.
- No studies reported on access to care, or drug interactions or other drug-related problems.

Characteristics of Studies (Appendix C, Table 1)

We identified 2 studies of pharmaceutical care for patients with cardiovascular disease or risk factors for cardiovascular disease,[11,12] 2 studies of care for patients with coronary artery disease,[13,14] and 2 studies of patients with congestive heart failure.[15,16] A total of 3,403 patients were enrolled; study sample sizes ranged from 117 to 2,170. Overall, we rated one study as low risk of bias, 3 as medium risk of bias, and 2 as high risk of bias.

The studies of patients with cardiovascular disease or risk factors included a 12-month RCT conducted in a cardiovascular risk reduction clinic (CRRC) at a VA Medical Center[11] and a retrospective cohort study from a university-affiliated cardiology group.[12] In the VA study, patients had achieved HbA1c, blood pressure, and LDL goals and were randomized upon discharge from the CRRC to either group medical visits facilitated by a clinical pharmacist, individual sessions with a clinical pharmacist, or standard primary care.[11] Both clinical pharmacist interventions were multifaceted. In the cohort study, the goal was to optimize blood pressure medication management and patients participated in either a multifaceted program based on a collaborative care model or usual care.[12] The patients were followed until they maintained therapy goals for several months.

One study of patients with coronary artery disease was a 2-year RCT with a multifaceted pharmacist intervention delivered via telephone compared to usual care.[14] The goal was to maintain lipid control. The second study was a retrospective cohort study from an outpatient pharmacy clinical service and focused on improving medication adherence.[13] Patients identified as non-adherent and not at clinical goals for HbA1c and LDL-C had either a pharmacist consult at the time of prescription pick-up or usual care. Follow-up was one year.

The studies of patients with CHF, both RCTs, involved multifaceted interventions – education, medication recommendations, and telephone follow-up in one[15] and protocol-driven education and medication monitoring in the other.[16] Both studies focused on optimizing heart failure

therapy. In one study, median follow-up was 6 months.[15] The other study included a 9-month intervention period and a 3-month post-intervention assessment.

Clinical Outcomes (Appendix C, Table 3)

Two studies (n=602) reported all-cause mortality, finding intervention and control groups to be similar.[14,15] However, in one of these studies, the primary outcome was a combination of all-cause mortality and non-fatal heart failure events.[15] There was a significant difference between groups for the composite outcome favoring the intervention group (OR 0.22 [95% CI 0.06, 0.63]).

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 3)

One of the CHF studies reported similar improvement in health-related quality of life from baseline for the intervention and control groups.[16] Satisfaction with pharmacy services improved significantly from baseline for the intervention group relative to the control group.[16]

Goal Attainment (Appendix C, Table 5)

The VA-based cardiovascular disease/risk factors RCT reported maintenance of HbA1c, blood pressure, and LDL goals.[11] Failure rates for HbA1c and blood pressure per quarter were significantly lower for intervention patients in either the individual or group pharmacist interventions relative to control. Adherence to LDL guidelines was lowest in the individual pharmacist intervention patients. In the cohort study of high cardiac-risk patients, blood pressure goals were achieved in a significantly higher percentage of patients in the intervention group.[12] In the study of patients with coronary artery disease, the study groups were similar in the percentages of patients maintaining LDL goals (either less than 100 mg/dL or less than 70 mg/dL) or blood pressure less than 130/80 mmHg.[14] Significantly more patients in the control group achieved the blood pressure goal of less than 140/90 mmHg. Neither of the CHF studies reported a goal attainment outcome. Goal attainment findings are summarized in Table 3.

Medications (Appendix C, Table 2)

Few studies reported on drug-related problems. A study of patients with coronary artery disease reported persistence with lipid-lowering therapy, finding the intervention and control groups to be similar.[14] Figure 4 is a forest plot of adherence outcomes from the RCTs. Another study, focused on adherence, reported a significantly lower medication possession ratio (MPR) at one year in the intervention group compared to control (0.70 vs 0.74) but the percentage of patients defined as adherent at one year was similar in the 2 groups (37% vs 38%).[13]

One of the CHF studies reported the fraction of target ACE inhibitor dose taken.[15] Patients in the intervention group were taking a significantly higher fraction of the target dose than were patients in the control group. The other CHF study reported the incidence of adverse events or medication errors to be similar for the intervention and control groups but higher refill adherence in the intervention group.[16]

Table 3. Goal Attainment - Cardiovascular Diseases[a] (6 studies)

Author, year	Attained Goals for HbA1c Levels	Attained Goals for Blood Pressure	Attained Goals for Lipid Levels
Spence, 2014[13]			
Taveira, 2014[11]	↑	↑	↔
Irons, 2012[12]		**↑**	
Olson, 2009[14]		↕[b]	**↔**
Murray, 2007[16]			
Gattis, 1999[15]			

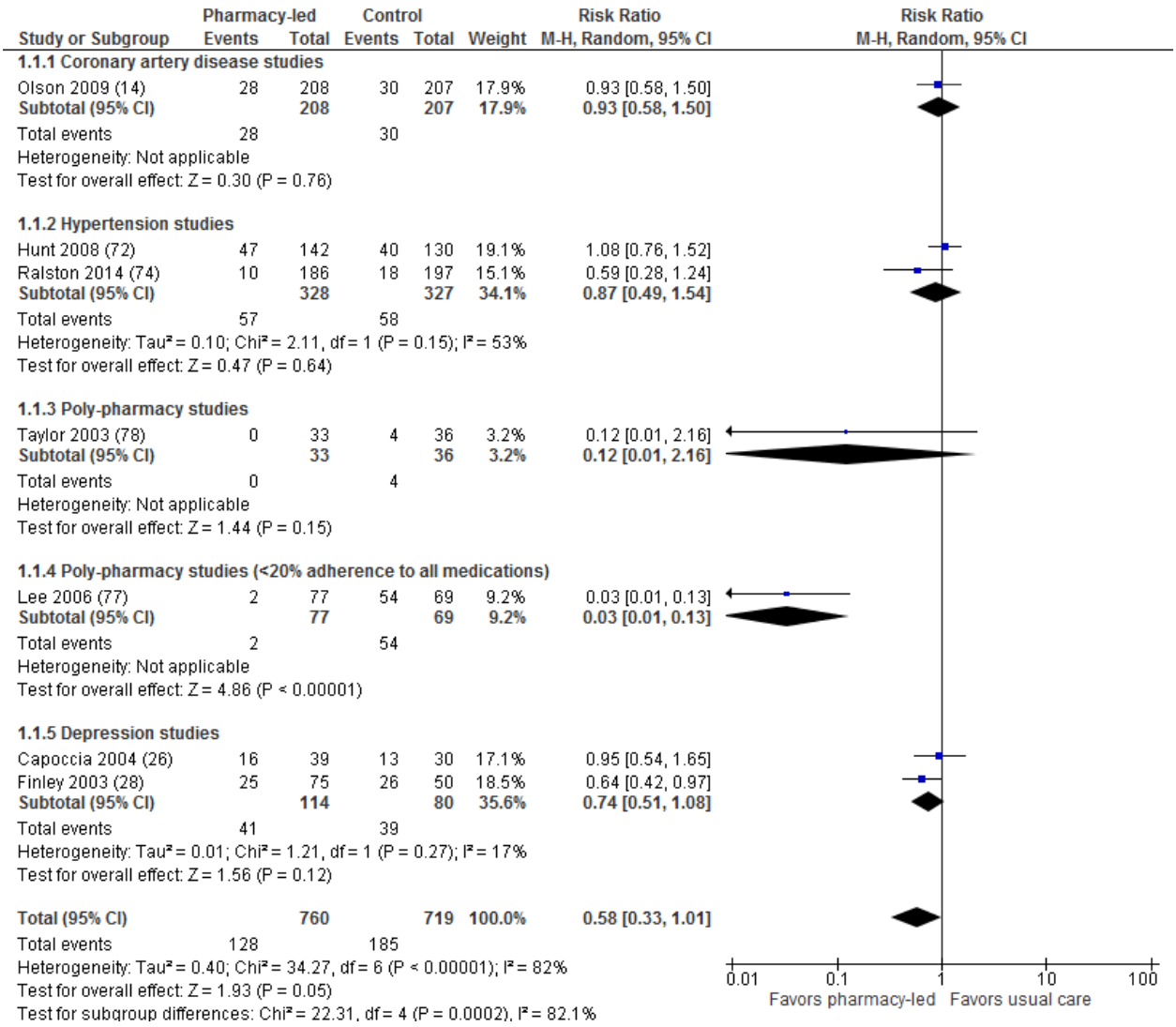
↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)
↔ = results not significant
↕ = mixed results
Bold indicates a study-defined primary outcome
[a] Cardiovascular disease or risk factors for cardiovascular disease, coronary artery disease, and congestive heart failure
[b] Goal of BP <140/90 mmHg reached by a significantly higher proportion of control group; proportion of patients in each group reaching goal of <130/80 mmHg was similar

The RCT enrolling patients with cardiovascular disease or risk factors assigned to individual or group pharmacist interventions reported no change in medications from baseline for patients in the individual intervention group but significantly increased use of blood pressure and anti-hyperglycemic medications in the group intervention patients. A significant decrease in cholesterol and anti-hyperglycemic medications from baseline was noted for the control group.[11] The cohort study of patients with cardiovascular disease or risk factors reported a significant difference in the number of antihypertensive medications with greater use in the intervention group.[12] One RCT of patients with CHF reported a similar percentage of patients receiving an ACE inhibitor at follow-up for the intervention and control groups. More patients in the intervention group were receiving an ACE alternative.[15]

Resource Use (Appendix C, Tables 3 and 4)

Each of the studies reported a measure of resource use. Results were mixed for office visits with no differences between intervention and control groups in primary care visits in the VA RCT,[11] while more clinic visits or blood pressure assessments outside of scheduled appointments were noted for the intervention group in a retrospective cohort study.[12] Two studies (one RCT from the VA and one cohort study) reported no differences between groups in urgent care/emergency department visits,[11,13] while a study of patients with CHF reported fewer all-cause emergency department visits in the intervention group but similar numbers of emergency department visits for heart failure between study groups.[16] Hospitalizations (reported in 4 studies) were similar between study groups[11,13,14,16] but one heart failure study reported a lower readmission rate in the intervention group.[15] Two studies reported costs outcomes. The one-time pharmacist consult to improve adherence resulted in cost savings such that approximately $5.79 was saved for every dollar spent on the intervention program.[13] This result was based on data from implementing the intervention for patients with diabetes and patients with coronary artery disease. A study of patients with CHF reported lower outpatient and inpatient costs in the intervention group; the statistical significance was not reported.[16] No studies reported on access to care.

Figure 4. Non-adherence to Prescribed Medications, Proportion of Patients (RCTs Only)



Chronic Kidney Disease (2 RCTs, 2 Cohort Studies)

Key Findings

- Pharmacist-led care
  - improved kidney disease-related quality of life at one year but not 2 years among patients at a university-affiliated dialysis center but resulted in similar quality of life for Veterans with CKD in primary care.
  - lowered medication use in the intervention group in the dialysis study,
  - increased use of anti-hypertensive medications in the VA study with intervention and control groups similar on blood pressure goal attainment,
  - resulted in similar all-cause mortality between groups in both studies, and
  - to manage anemia due to CKD was associated with a lower weekly dose of EPO (k=1), more medication adjustments if hemoglobin levels were low (but not high) (k=1), cost savings (k=2 s), and better attainment of target hemoglobin (k=2) and iron

saturation values (k=1) versus usual care; intervention and control sites reported similar rates of adverse events (k=1).

- No studies reported on office or emergency department visits, access to care, or drug interactions or other drug-related problems.

Characteristics of Studies (Appendix C, Table 6)

Four studies (reported in 6 papers) enrolled patients with CKD.[17-19,20,21,22] One was a medium risk of bias RCT conducted at a university-affiliated dialysis clinic and focused on drug-related problems, drug use and costs, and hospitalizations.[18] Another was a high risk of bias retrospective cohort conducted at a nephrology clinic and addressing use of epoetin alfa (EPO).[19] A more recent low risk of bias RCT, based in VA community-based outpatient clinics (CBOCs) focused on care for patients with CKD, especially blood pressure control.[20] The last was a medium risk of bias cohort study done a VA Medical Centers.[21,22] The goal was improved quality of erythropoiesis-stimulating agent (ESA) prescribing for non-dialysis dependent CKD patients.

The interventions varied. In a dialysis clinic-based RCT, pharmacists conducted one-on-one in-depth drug therapy review meetings with patients every 8 weeks.[18] Pharmacists also provided health care provider and patient education. The comparator was usual care which included drug therapy reviews by dialysis nursing staff. The study enrolled 57 intervention group and 47 control group patients. However, 53% of the intervention group and 45% of the control group did not complete the 2-year study due to death, transplant, or transfer to another dialysis facility.[18] In the RCT based in VA CBOCs, the goal was increased pharmacist interaction with patients (primarily telephone-based) and communication of recommendations to primary care physicians.[20] The one-year study enrolled 2,199 patients; 870 had blood pressure values greater than 130/80 mmHg at baseline. Among the cohort studies, one (n=141) involved a protocol-driven program to manage anemia of CKD.[19] Maximum follow-up was one year. Patients in the intervention group also received intravenous sucrose while the control group received only EPO. The other compared clinics (10 clinics, n=314) where pharmacists managed dosing and monitored ESA therapy to clinics (6 clinics, n=167) where physicians managed care.[21,22] Follow-up was 6 months.

Clinical Outcomes (Appendix C, Table 8)

Both RCTs reported clinical outcomes. In the larger study (n=2,199), at one year follow-up, all-cause mortality was 4.7% in the intervention group and 6.6% in the control group (P=.06).[20] In the second study (n=104), all-cause mortality was 26% at 2 years in both the intervention and control groups.[18] The cohort study comparing pharmacist-managed ESA clinics to usual care clinics reported that adverse event rates (thromboembolic events, heart failure, uncontrolled hypertension) were similar between the clinic types.[21]

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 8)

The study of drug-related problems found a significant difference in health-related quality of life between groups at one year (with higher quality of life in the intervention group) but no difference was observed at 2 years.[17] The study of care for CKD found the intervention and control groups had similar results for measures of quality of life.[20] This study also reported that 92% of the intervention patients surveyed responded that the pharmacists provided useful information and they would recommend the program to others.[20]

Goal Attainment (Appendix C, Table 10)

The EPO study reported a significantly higher percentage of measured hemoglobin and iron saturation values within target ranges in the intervention groups (Table 4).[19] Similarly the study of ESA prescribing found a higher proportion of patients with hemoglobin values within range in the pharmacist-managed group.[21] The RCT of CKD care reported the groups were similar in blood pressure goal attainment.[20]

Table 4. Goal Attainment - Chronic Kidney Disease (4 studies)

Author, year	Attained Goals for Iron Saturation	Attained Goals for Hemoglobin	Attained Goals for Blood Pressure
Pai, 2009[18]			
Bucaloiu, 2007[19]	↑	↑	
Aspinall 2012[21]		↑	
Cooney 2015[20]			↔

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)
↔ = results not significant

Medications (Appendix C, Table 7)

The RCT focused on drug-related problems reported results only for the intervention group.[18] Of 530 identified drug-related problems, 14% were related to sub-therapeutic dosage, 25% for untreated indications, and 5% for overdose. The RCT of CKD care found patients in the intervention group were prescribed significantly more classes of anti-hypertensive drugs than the control group. The intervention and control groups were similar in medication adherence.[20] The ESA prescribing study found significantly more adjustments to medications if hemoglobin levels were low in the intervention clinics; the frequency of medication adjustments if hemoglobin levels were high was similar in the intervention and usual care clinics.[21]

Resource Use (Appendix C, Tables 8 and 9)

The RCT focused on drug-related problems reported significantly fewer all-cause hospitalizations, lower number of medications, and lower mean drug costs (significantly lower at one of the drug reviews) in the intervention group.[18] The EPO study reported a significantly lower weekly dose of EPO in the intervention group with estimated annual cost savings per patient of $3,860.[19] The study of pharmacist-managed ESA clinics modeled costs over 5 years and found lower costs (drug, laboratory test, clinic visit, and hospitalization costs were included) in the pharmacist-managed clinics.[22] No study reported access to care.

Chronic Obstructive Pulmonary Disease (1 RCT)

Key Findings

- Multifaceted pharmacist-led care from 8 VA Medical Centers
  - resulted in health-related quality of life, number of new medications, number of emergency department visits, and a rate of hospitalization that were similar to usual care,
  - decreased office visits, and
  - resulted in mixed findings for patient satisfaction (*ie,* significant differences on some subscales).

- Effects on drug-related problems were reported only for the intervention group.
- All-cause mortality, disease-specific clinical events, access to care, and costs were not reported.

Characteristics of Studies (Appendix C, Table 11)

One medium risk of bias RCT (reported in 2 papers), conducted at 8 VA Medical Centers, enrolled 98 patients with COPD.[23,24] The intervention consisted of regularly scheduled therapeutic and educational interventions with pharmacists responsible for implementing the care plan, educating and counseling patients, and performing patient assessments. The comparator was usual care. Outcomes were assessed at 6 months follow-up.

Clinical Outcomes (Appendix C, Table 13)

No clinical outcomes were reported.

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 13)

A global symptom assessment and quality of life were similar for intervention and control groups although bodily pain was significantly worsened from baseline to 6 months in the control group.[23,24] On a 10-item Pharmaceutical Care Questionnaire, intervention group patients had more favorable responses than control group patients for all items; the difference was significant for 7 of the 10 items.

Goal Attainment (Appendix C, Table 10)

No goal attainment outcomes were reported.

Medications (Appendix C, Table 12)

The study reported drug-related problems for the intervention group only.

Resource Use (Appendix C, Tables 13 and 14)

There were significantly fewer office visits in the intervention group but similar incidence compared to usual care control for emergency department visits, hospitalizations, or new medications.[23,24] Access to care was not reported.

Depression (3 RCTs, 1 non-RCT)

Key Findings

- Pharmacist-led care
  - was similar to usual care for depressive symptoms and health-related quality of life,
  - was similar to usual care for medication adherence (2 RCTs reporting); self-reported use of antidepressant medications and changes in antidepressant medications were more frequent in the pharmacist-led care groups,
  - resulted in numbers/rates of primary care or urgent care visits that were similar to usual care, and
  - increased patient satisfaction with availability of advice.
- All-cause mortality, hospitalizations, costs, inappropriate prescriptions, drug interactions, and other drug-related problems and harms were not reported.

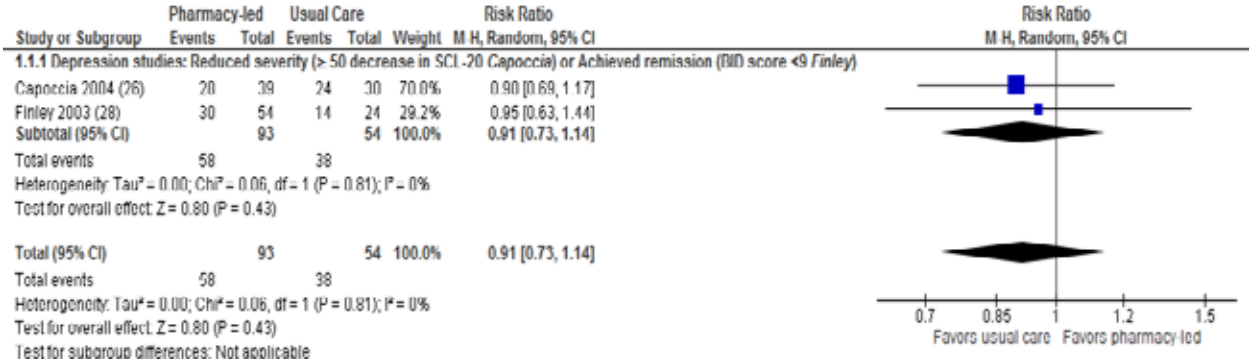
Characteristics of Studies (Appendix C, Table 16)

Three RCTs of pharmacists' interventions in primary care clinics (reported in 4 articles) were reviewed.[25-28] In addition, we included a non-randomized comparison group pilot study.[29] A total of 926 patients were enrolled with samples sizes ranging from 74[26,27] to 507.[25] None of the studies was conducted at VA facilities. All of the studies tested multifaceted interventions provided in multiple contacts over 6 to 12 months by experienced Doctors of Pharmacy (PharmD). The pharmacists' interventions included medication histories and reviews, patient education and frequent monitoring (primarily by telephone), dose titration, and changes in antidepressant medications. The interventions were compared to usual care. In one study, usual care included access to services of the same clinic pharmacists.[26,27] The targeted patient population was newly diagnosed or treated episodes of depression. Patients with complicating mental co-morbidities were excluded from all studies. The primary patient outcome in 2 of the RCTs was one or more measure of symptoms of depression.[25-27] The third RCT focused on the intermediate outcome of antidepressant adherence, but included a measure of symptoms of depression.[28] The non-randomized study focused on medication adherence, patient satisfaction, and resource utilization.[29] We rated one study as low risk of bias, 2 as medium risk of bias, and one as high risk of bias.

Clinical Outcomes (Appendix C, Table 18)

Two RCTs looked at reduction in severity of depression as a clinical outcome – a reduction of at least 50% in a symptom score.[26,28] The pharmacist-led intervention and usual care control groups were similar (Figure 5). The pooled risk ratio for at least 50% reduction in a symptom score in the intervention group compared to usual care was 0.91 (95% CI 0.73, 1.14). One of the studies also reported the percent achieving remission (a Brief Inventory for Depressive Symptoms score of less than 9); the study groups were similar.[28]

Figure 5. Clinical Outcomes for Depression Trials



Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 18)

All 3 RCTs reported health-related quality of life measures, finding groups to be similar.[25-28] Each of the studies reported on patient satisfaction. One reported that intervention and control groups expressed similar satisfaction with depression care and overall health care.[26] Two reported mixed results for a single question about patient satisfaction with treatment of depression, finding either higher satisfaction in the intervention group[28] or similar satisfaction in

the 2 groups.[29] The fourth study reported that patients expressed high satisfaction with the pharmacist intervention but results for the intervention and control groups were not reported separately.[25]

Goal Attainment (Appendix C, Table 20)

No goal attainment outcomes were reported.

Medications (Appendix C, Table 17)

Two RCTs reported medication adherence (Figure 4). One observed similar adherence between pharmacist-led care and usual care.[26] The second, which specified adherence as the primary study endpoint, reported significantly greater adherence in the intervention group.[28] However, the medication possession ratio was similar in the 2 groups (0.83 vs 0.77, P=.26).[28] The largest RCT reported a significant 12% higher percentage of intervention group patients on antidepressants at 3 and 6 months.[25] Two studies (one RCT and the non-randomized trial) reported more changes in antidepressants in the intervention groups.[28,29] The non-randomized study reported a significantly higher medication possession ratio at 6 months and significantly higher use of antidepressants at 3 months in the intervention group.[29]

Resource Use (Appendix C, Tables 18 and 19)

Two RCTs reported the intervention and control groups were similar in primary care provider visits[26,28] although the non-randomized study reported a significantly greater decrease in primary care provider visits in the pharmacist-led care group.[29] In 2 RCTs reporting, there were no differences in urgent care visits.[26,28] No study reported hospitalizations. Both the RCT and the non-randomized pilot study from the same research group reported greater availability of advice in the intervention groups.[28,29] One study reported drug costs were similar between groups.[26]

Diabetes Mellitus (12 RCTs, 2 CCTs, 10 Cohort Studies)

Key Findings

- Pharmacist-led care
  - resulted in all-cause mortality, disease-specific clinical events, and health-related quality of life that was similar to usual care, although few studies reported these outcomes,
  - improved rates of goal attainment for HbA1c, blood pressure, and lipids; the 3 studies in VA settings reported increased attainment of HbA1c and blood pressure goals in patients receiving pharmacist-led care,
  - resulted in significantly higher numbers and/or doses of medications, and
  - resulted in resource use (office visits, urgent care or emergency department visits, and hospitalizations) that was similar to usual care.
- One study reported access to care favoring the intervention group; no studies reported drug interactions or other drug-related problems.

Characteristics of Studies (Appendix C, Table 21)

We included 24 trials (12 RCTs or cluster RCTs, 2 CCTs, 10 cohort studies) in 25 papers of pharmacist-led care interventions for patients with diabetes mellitus. Four were conducted at VA facilities.[30-32,33,34] A total of 17,716 patients were enrolled. All studies used multifaceted

interventions. In one study the intervention consisted of a single session,[13] one study did not specify the frequency of the intervention,[35] and the remaining studies were conducted over one to 24 months. The pharmacist had some level of collaboration with other healthcare professionals in 19 studies, typically the patient's primary care provider (16 studies). The comparator groups received usual care generally delivered by their primary care provider. In all studies, the primary outcomes included physiological markers (blood pressure, HbA1c, or cholesterol) – either achieving control, change in level, or rate of testing. Fifteen studies were rated medium risk of bias; of the remaining 9 studies, 5 were rated low risk of bias and 4 as high risk of bias.

Clinical Outcomes (Appendix C, Table 23)

Four studies reported on clinical events.[36-39] One study reported the pharmacist-led intervention and usual care groups were similar for rates of hypoglycemic or hypotensive episodes.[39] Another study reported an increase in hypoglycemic events in the intervention group compared to the usual care group but significance could not be determined.[37] One study reported one severe hypoglycemic event in the intervention groups but events were not documented in the control group.[36] Another study reported no adverse events caused by the study protocol.[38]

Three studies assessed mortality with 2 reporting the study groups were similar in all-cause mortality[32,39] and one reporting no diabetes-related deaths.[30]

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 23)

No significant findings were reported for health-related quality of life.[32,37,40] Three studies reported patient satisfaction with care with 2 of the 3 reporting a significantly higher level of satisfaction in the intervention groups.[39,40]

Goal Attainment (Appendix C, Table 25)

Most of the included studies measured attainment of goals for HbA1c, blood pressure, and lipid levels (Table 5, Figure 6). Fifteen studies reported attainment of HbA1c goals, typically an HbA1c less than 7%. Twelve studies found improved goal attainment in the intervention groups compared to the usual care groups although the difference was significant in just 8 of the studies.[30-32,36,41-44] Three found lower goal attainment in intervention groups compared to controls with significant differences in 2 of the studies.[45,46] All 3 VA studies reporting on HbA1c goal attainment showed that pharmacist-led care significantly improved goal attainment.[30-32] Pooled results from the RCTs (Figure 6) showed significantly greater HbA1c goal attainment in the intervention groups (RR 1.83 [95% CI 1.44, 2.33]).

Twelve studies reported on attainment of blood pressure control, typically defined as blood pressure less than 130/80 mmHg. Of these, 10 showed increased attainment of blood pressure goals in the intervention groups compared to controls with 6 finding significant differences.[31,32,40,42-44] Two studies found study groups were similar.[41,45] All 3 VA studies reporting this outcome saw increased goal attainment in patients in the intervention group compared to patients in the control group with significant results in 2 studies.[31,32]

Lipid goal attainment (LDL-C <100mg/dL) was measured in 11 studies. Pharmacist-led care increased goal attainment compared to usual care with significant findings in 6 studies.[42,43,45-48] The 3 VA studies found the study groups were similar.[30-32]

Medications (Appendix C, Table 22)

Thirteen studies reported number and/or dose of medications. In 9 studies, patients in intervention groups had significantly higher medication use than patients in control groups.[30-32,38-40,45,48,49] Two studies reported medication use was similar between groups [41,46] and significance was not reported for 2 studies.[36,47] All 3 of the studies at VA facilities reported a significant increase in medication use and/or dose in patients receiving pharmacist-led care.[30-32] Five studies reported on use of medications for diabetes (*eg,* insulin). All 5 found significantly more medication use in patients being cared for by pharmacists.[30-32,36,49] Two reported on hypertension medications and found significantly higher medication use and/or dose in intervention group patients as compared to controls.[30,32] Four studies reported on lipid medications with 3 finding significantly higher use in the intervention group[31,32,48] and one reporting no difference. [30]

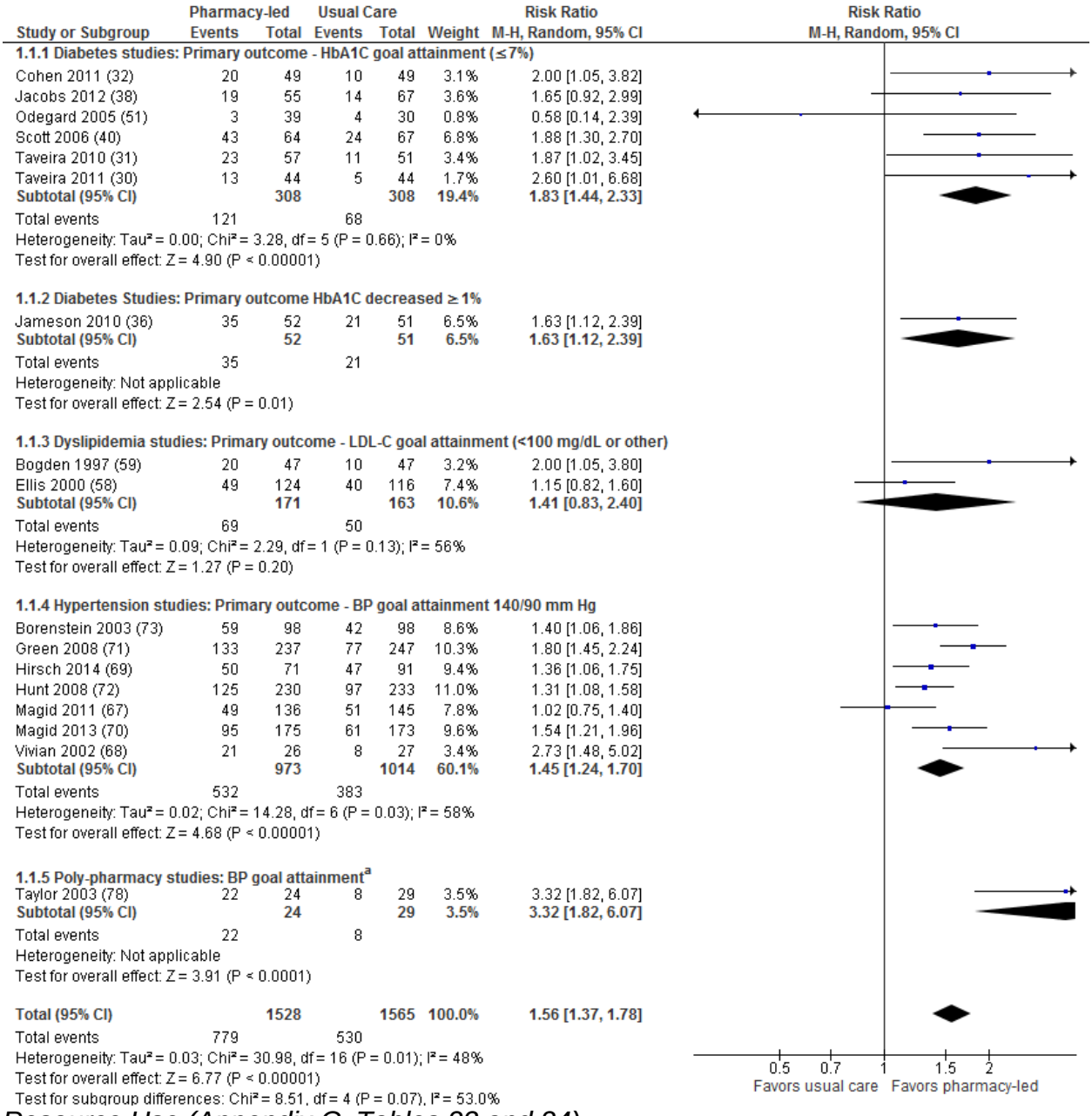
Table 5. Goal Attainment - Diabetes Mellitus (24 studies)

Author, year	Attained goals for HbA1c levels	Attained goals for blood pressure	Attained goals for lipid levels
McAdam-Marx 2015[53]			
Skinner 2015[35]			
Chung, 2014[50]			
Spence, 2014[13]			
Brummel, 2013[46]	**↓**[a]	**↔**	**↑**[+]
Ip, 2013[43]	**↑**	**↑**	**↑**
Jacobs, 2012[38]	**↔**	**↔**	**↔**
Salvo, 2012[49]	↔		
Cohen, 2011[32]	**↑**	**↑**	**↔**
Padiyara, 2011[45]	↓	↔	↑
Pape, 2011[48]	↔	↔	**↑**
Taveira, 2011[30]	**↑**	↔	↔
Heisler, 2010/2012[33,34]			
Jameson, 2010[36]	↑		
Johnson, 2010[42]	**↑**	↑	↑
Taveira, 2010[31]	**↑**	**↑**	**↔**
Fox, 2009[47]			**↑**
Scott, 2006[40]	↔	↑[b]	
Odegard, 2005[51]	↔		
Rothman, 2005[39]			
Shane-McWhorter, 2005[41]	↑	↔	↔
Stroup, 2003[52]			
Kelly, 2000[44]	↑	↑[b]	
Jaber, 1996[37]			

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)
↓ = significantly higher proportion of control group reached goal compared to intervention group (P<.05)
↔ = results not significant
[+] = significant change from baseline
Bold indicates a study-defined primary outcome
[a] HbA1c goal attainment was significantly improved from baseline to end of study and end of follow-up by intervention but at the end of follow-up the proportion of patients at goal HbA1c was significantly lower in the intervention group.
[b] Significantly more people in the intervention group met the goal for systolic blood pressure but groups were similar for diastolic blood pressure.

No studies reported on ineffectiveness or drug interactions. Only one study reported on medication inappropriateness finding mean medication appropriateness index scores were similar to usual care after 6 or 12 months of pharmacist-led care.[51] Four studies measured non-adherence[13,32,35,51] finding that patients receiving pharmacist-led care had higher adherence to their prescribed regimens; the difference was significant in 2 of the studies.[13,35] Out of 6 studies that measured aspirin use, 2 found significantly higher use in patients receiving care from pharmacists,[39,45] 2 found groups to be comparable,[31,46] and 2 did not report significance.[40,41] Two studies looked at the total number of medications that patients were prescribed and found groups were similar.[38,47]

Figure 6. Goal Attainment for Diabetes, Dyslipidemia, Hypertension, and Polypharmacy Studies Based on Primary Outcome (RCTs Only)



Resource Use (Appendix C, Tables 23 and 24)

Six studies measured office visits,[30,32,34,39,51,53] including 3 studies in VA settings.[30,32,34] Office visits were similar between intervention and control groups in 3 studies while one found increased outpatient utilization in the intervention group.[53] Seven studies looked at hospitalizations with similar results for intervention and control groups.[13,30,34,37,39,50,52,53] Two studies reported decreased urgent care or emergency room visits in intervention group patients compared to control group patients[13,52] while 6 other studies found study groups were similar.[30,34,39,40,50,53] One study found that patients under a pharmacist's care were significantly more satisfied with their ability to reach somebody in an emergency.[48] Three studies reported cost outcomes with one finding a lower increase in total patient charges (inpatient and outpatient)

over the study period for the intervention group[53] and 2 not reporting the significance of their findings.[13,47]

Dyslipidemia (2 RCTs, 2 CCTs, 3 Cohort Studies)

Key Findings

- Pharmacist-led care
  - improved goal attainment (typically LDL < 100 mg/dL) compared to usual care although pooled results from 2 RCTs showed groups were similar,
  - was associated with increased medication use; one study reported adherence in the intervention group but not the usual care group, and
  - led to mixed results for office visits and similar results for urgent care or emergency department visits and costs as usual care.
- No studies reported other clinical outcomes (*ie,* mortality, disease-specific clinical events, health-related quality of life, and patient satisfaction), hospitalizations, access to care, inappropriate prescriptions, or drug interactions or other drug-related problems.

Characteristics of Studies (Appendix C, Table 26)

We included 7 studies (total n=1,834) of pharmaceutical care for dyslipidemia.[54-60] There was one RCT,[59] 2 controlled clinical trials,[57,60] one prospective cohort study,[55] and 2 retrospective cohort studies.[54,56] The remaining study was a sub-study of an RCT.[58] Follow-up ranged from 4 weeks to 46 months. Four studies were conducted at VA clinics.[54,56,58,60] All studies enrolled patients from primary care (*ie,* family medicine, general medicine) clinics. In one study, although the intervention group consisted of family medicine center patients, the control group was from family medicine, cardiology, and endocrinology clinics.[55] We rated 3 studies as medium risk of bias and 4 as high risk of bias.

Intervention components included medication evaluation,[54,56,58,59] medication prescription and adjustment,[54,56-58] therapeutic conversion,[55] ordering and reviewing of laboratory results,[54,57,59] patient education,[55,57,60] follow-up contacts,[54,56,60] physician collaboration,[55,57,59,60] identification and prevention of drug-related problems,[58] and referral to other resources (*ie,* smoking cessation).[57]The comparator was usual care in all studies.

Clinical Outcomes (Appendix C, Table 28)

None of the studies reported all-cause mortality or clinical events.

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 28)

None of the studies reported health-related quality of life or patient satisfaction outcomes.

Goal Attainment (Appendix C, Table 30)

Each of the studies reported a goal attainment outcome (Table 6, Figure 6). Significantly more patients in the intervention groups achieved LDL goals in 5 studies.[54,56,57,59,60] Another study reported a significant increase in goal attainment from before to after therapeutic conversion in the intervention group and a significant decrease during that time period in the control group.[55] The last study reported significant improvements in goal attainment for both the intervention and control groups but groups were similar at the end of the study.[58] Pooled results from the 2 RCTs

(Figure 6)[58,59] showed the effect of pharmacist-led care on goal attainment was similar to usual care (RR 1.41 [95% CI 0.83, 2.40]).

Table 6. Goal Attainment - Dyslipidemia (7 studies)

Author, year	Attained Goals for Lipid Levels
Smith, 2013[54]	↑
Miller, 2008[55]	↑+
Mazzolini, 2005[56]	↑
Straka, 2005[57]	↑
Ellis, 2000[58]	↔
Bogden, 1997[59]	↑
Konzem, 1997[60]	↑

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)
↔ = results not significant
+ = significant change from baseline
Bold indicates a study-defined primary outcome

Medications (Appendix C, Table 27)

Number and/or dose of medications was significantly higher in the pharmacist-led care groups compared to control groups in 3 of 5 studies reporting this outcome.[56,57,60] Significance was not reported in 2 other studies[55,59] One study reported significantly more medication interventions per patient in the intervention group.[54] The study of therapeutic conversion reported more patients in the intervention group received an equivalent dose post-conversion while more patients in the control group received a lower dose.[55] One study reported compliance for the intervention group but not the control group.[60]

Resource Use (Appendix C, Tables 28 and 29)

Three studies reported office visits with 2 finding intervention and control groups were similar[54,56] and one finding more office visits in the intervention group.[59] One study reported that the frequencies of emergency department visits were similar between groups.[59] None of the studies reported hospitalizations. Two studies reported costs finding similar changes from the baseline period between intervention and control groups for hospitalization, clinic visit, and drug costs[58] or medication costs.[59]

Hypertension (13 RCTs, 1 CCT, 1 Case-Control Study)

Key Findings

- Pharmacist-led care
  - resulted in similar health-related quality of life as usual care; patient satisfaction results were mixed and few studies reported other clinical outcomes,
  - increased medication use but adherence was similar to usual care,
  - led to mixed results for resource use outcomes including office visits and costs; few studies reported urgent care or emergency room visits, and
  - resulted in patient perceptions similar to usual care for "had problems getting needed care."

- No studies reported drug interactions or other drug-related problems; one study reported inappropriate medications for the intervention group but not the control group.

Characteristics of Studies (Appendix C, Table 31)

We identified 13 randomized controlled trials (RCTs) reported in 15 papers that evaluated the effect of pharmacist-led care for the management of uncontrolled hypertension (HTN). Four trials were cluster-randomized (*ie,* trials that randomized clinics and not patients).[61-64] We also included one controlled clinical trial[65] and one case-control study.[66] The studies enrolled a total of 6,278 patients. Four studies included patients from Veterans Affairs Medical Centers.[23,24,66-68]

In 5 studies, pharmacists had the ability to initiate and change medical therapy for HTN management although some physician oversight may have been involved.[62,66-70] In 6 studies, pharmacists provided guidance and made recommendations to the patient's physician or worked directly with the physician (team-based or co-management care) on how to best implement the medical therapy for HTN management.[61,63,64,71-73] Usual care was typically continued care with the patient's primary care physician although in one study, some control group patients were provided with home blood pressure monitors.[71,74] Study periods ranged from 6 to 24 months. One study also included a 6-month follow-up period after the 12-month intervention to observe the maintenance of any affects following the discontinuation of the intervention.[62] Overall risk of bias was medium; 2 studies were rated low risk of bias.[66,71,74]

Clinical Outcomes (Appendix C, Table 33)

Overall, the included trials were short-term, underpowered, or not designed to evaluate the impact of a pharmacist component of patient care on all-cause mortality or other clinical events. One trial reported deaths during the study period – one in the pharmacist component arm due to cardiac arrest and none in the usual care arm.[71] Other trials reported clinical events in the intervention and control groups were similar,[62,64,71] or the significance of the findings was not provided.[69,75]

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 33)

Patient satisfaction with care was evaluated in 8 trials. Two studies reported a clinical patient satisfaction outcome. One study reported a significantly higher percentage of patients reporting high satisfaction with their hypertension care in the pharmacist component group compared with the usual care group (58% vs 42%, P< .001).[70] The other reported the percentage of patients very satisfied with pharmacy services to be similar between groups (88% vs 68%, P=.098).[68] The other studies reported scale score changes with mixed results.[23,24,62,69,71,72,74] Health-related quality of life was evaluated in 7 trials.[23,24,62,65,68,71,72,75] Patient health-related quality of life did not differ between the pharmacist component and usual care groups.

Goal Attainment (Appendix C, Table 35)

Nearly all trials reported the proportion of patients who attained controlled BP, typically defined as a systolic BP <140 mm Hg and diastolic BP < 90 mm Hg (Table 7, Figure 6). Ten studies reported greater goal attainment in the intervention group compared to the usual care group [62-64,66,68-73] while 3 reported the groups to be similar.[61,65,67] Pooled data from 7 RCTs showed the proportion of patients who attained controlled BP was significantly greater in the pharmacist-led care group (54%) compared with the usual care group (38%) (RR 1.45 [95% CI 1.24 1.70])

(Figure 6). There was a moderate level of heterogeneity (I^2 = 58%) Similar to the findings for all patients, greater attainment in controlled blood pressure was also observed in the pharmacist intervention group for the subgroup of patients with diabetes with or without chronic kidney disease.[63,64,70]

Table 7. Goal Attainment - Hypertension (15 studies)

Author, year	Attained Goals for Blood Pressure
Carter 2015[61]	↔
Zillich 2015[66]	↑
Hirsch, 2014[69]	↑
Magid, 2013[70]	↑
Margolis, 2013[62]	↑
Magid, 2011[67]	↔
Carter, 2009[63]	↑
Carter, 2008[64]	↑
Green, 2008, Ralston 2014[71,74]	↑
Hunt, 2008[72]	↑
Borenstein, 2003[73]	↑
Vivian, 2002[68]	↑
Okamoto, 2001[75]	
Solomon 1998, Gourley, 1998[23,24]	
Erickson, 1997[65]	↔

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)
↔ = results not significant
Bold indicates a study-defined primary outcome

Medications (Appendix C, Table 32)

No trial reported inappropriate dosage/prescription or omission, ineffectiveness, or drug interactions for both the pharmacist-led care group and the usual care group. One study reported drug-related problems including need for additional therapy, need for dose increase, and adverse drug reaction data for intervention group.[69] Poor or less than perfect adherence to the prescribed regimen, determined from the inverse of typically self-reported good adherence, was not significantly different between study groups in 6 trials.[62-64,67,68,71,72,74] One trial reported better compliance in the intervention group[23,24] and 2 trials only reported results for the intervention group.[69,70] Pooled data from 2 RCTs (Figure 4) showed no difference in adherence (RR 0.87 [95% CI 0.49, 1.54]). The case-control study reported that medication possession ratios and the percentage of patients with possession ratios of at least 80% for all blood pressure medications were similar between the intervention and control groups.[66]

Significant increases in medication use associated with a pharmacist component in patient care were reported in 9 trials.[61-64,67,70-73] Compared with usual care patients, pharmacist component patients were prescribed more antihypertensive medications during the intervention intervals. Four trials reported similar medication use between intervention and control groups.[65,66,68,75]

Resource Use (Appendix C, Tables 33 and 34)

Health care utilization results were mixed. Three trials reported patients in the pharmacist-led care groups had significantly fewer primary care visits compared with usual care patients.[69,72,73] However, in one trial, with the addition of pharmacy visits, total visits were comparable with or greater than those in the usual care group.[72] Four trials reported the numsber of primary care visits to be similar between study groups[65,68,70,71] and one reported a significantly greater number of clinic visits in the pharmacist-led care group.[75] Pharmacist-led care and usual care were similar in the number of urgent care or emergency room visits and hospitalizations although few studies reported these outcomes.

Four trials provided estimates of costs associated with pharmacist-led care. One study estimated that direct program costs would total about $1,350 per patient but did not provide costs for usual care.[62] In a publication[76] based on data from a cluster randomized trial,[64] the adjusted total costs per patient were $775 in the pharmacist-led care group compared to $446 in the control group (difference $329, P<.001). However, a cost-benefit analysis was not done to determine if the financial savings related to potentially reduced morbidity and mortality achieved from lower blood pressure outweighed the costs of the pharmacist component. Another study reported that the average provider visit costs per patient were lower in the pharmacist component group compared to usual care ($160 and $195, respectively; P=.04).[73] These costs were based on average number of visits to the primary care physician during the study which were lower in the pharmacist-led care group (3.4 compared with 6.6 for usual care patients; P<.01) and lower provider visit costs for pharmacists ($20 for a 30-minute appointment) than physicians ($35 for a 15-minute appointment). Average monthly drug costs were similar at the end of the study period. The fourth study reported drug costs per patient and total costs per patient did not differ between study groups.[75] Clinical visit costs (based on the salary of the provider – pharmacist or physician) were significantly higher in the pharmacist-led care group.

Polypharmacy/High Risk for Drug-related Problems (3 RCTs)

Key Findings

- Pharmacist-led care
  - resulted in health-related quality of life; patient satisfaction, and rates/numbers of disease-specific clinical events that were similar to usual care; goal attainment was improved,
  - resulted in similar medication use as usual care; results were mixed for medication adherence; significance of other medication findings could not be determined, and
  - increased the number of office visits compared to usual care but decreased use of urgent care facilities; results were mixed for hospitalizations and costs.
- No studies reported all-cause mortality or access to care.

Characteristics of Studies (Appendix C, Table 36)

We identified 3 RCTs (in 4 papers) of clinical pharmacist interventions in primary care clinics for patients judged to be at high risk for drug-related problems.[77-80] The studies enrolled a total of 1,282 patients (range 69 to 1054). One study was rated low risk of bias and 2 were rated medium risk of bias. Two studies targeted ambulatory adults with multiple risk factors for drug-related problems[78-80] and one study targeted ambulatory adults aged 65 years or older with polypharmacy (4 or more medications).[77] Patients were considered at high risk due to use of

multiple medications, multiple changes in medications in the past year, multiple concurrent diseases, a history of non-compliance, and/or use of medications requiring therapeutic monitoring. One study was conducted at VA primary care clinics.[79,80] Patients were excluded from the trials if they had cognitive impairment, lived in nursing homes, had life expectancy less than 12 months, or had other problems with verbal or written communication. All 3 studies tested multifaceted interventions delivered by a clinical pharmacist over 6- to 12-month periods. The comparator groups received routine care by physicians and nurses in clinic without contact with a clinical pharmacist. In one of the studies, the RCT phase followed a 6-month cohort phase in which all patients received the intervention. Patients were then randomized to continue the intervention or return to usual care follow-up.[77]

Clinical Outcomes (Appendix C, Table 38)

No study reported all-cause mortality. In one study, the percentage of patients with at least one "medication misadventure" was similar between the study groups (2.8% intervention vs 3.0% control, P=.73).[78]Another study noted less decline in the "change in health" component in the intervention group patients but the difference between intervention and usual care groups was not clinically meaningful (defined as a 5-point difference).[80]

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 38)

Two studies, including the VA-based study, found health-related quality of life (assessed with the SF-36) to be similar between intervention and usual care groups.[78,80] The VA study reported no differences in patient satisfaction at baseline or over the course of the study.[80] Another study reported significantly higher pharmacy-related satisfaction in the usual care group although the reporting is unclear.[78]

Goal Attainment (Appendix C, Table 40)

One study found statistically significant improvements in goal attainment for hypertension, diabetes mellitus, and dyslipidemia but similar anticoagulation goal attainment between groups (Table 8, Figure 6).[78]The trial comparing on-going pharmacist intervention to usual care found a higher percentage of patients with medication adherence at greater than 80% at the end of the randomized trial phase in the intervention group.[77] The VA study did not report goal attainment.

Table 8. Goal Attainment - Polypharmacy/High Risk (3 studies)

Author, year	Attained Goal for Medication Adherence	Attained Goal for Hypertension	Attained Goal for Diabetes	Attained Goal for Dyslipidemia	Attained Goal for Anticoagulation
Lee, 2006[77]	↑				
Taylor 2003[78]		**↑**	**↑**	**↑**	**↔**
Malone 2000 and 2001[79,80]					

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)
↔ = results not significant
Bold indicates a study-defined primary outcome

Medications (Appendix C, Table 37)

In one study, pharmacist-led interventions were associated with fewer inappropriate dosage prescriptions (13% vs 64%), fewer inappropriate indication prescriptions (16% vs 48%), fewer ineffective prescriptions (14% vs 45%), and fewer drug-drug (6% vs 23%) and drug-disease (9% vs 20%) interactions at 12 months compared to the usual care group.[78] The statistical significance of the findings was not reported. Study groups were similar for compliance (100% intervention, 89% usual care) (Figure 4). The study of improvement maintenance reported significantly greater medication adherence in the group that continued the intervention compared to the group that received usual care (Figure 4).[77] The VA study reported groups were similar for the increase in drug fills over the course of the study.[79,80] Another study reported mean number of anti-hypertensive medications was similar[77] while the third study reported a significantly lower number of prescribed medications in the intervention group.[78]

Resource Use (Appendix C, Tables 38 and 39)

A significant increase in office visits but not hospitalizations was reported in the VA pharmacist-led care group compared to VA usual care.[79,80] Another study reported a significant decrease in urgent care visits and hospitalizations during the study period in the intervention group compared to the usual care group.[78] Cost outcomes included a similar mean cost for the pharmacist intervention (including clinic visits, drug costs, laboratory costs, and hospitalizations) compared to usual care in the VA study[79,80] and a determination that a lower percentage of patients in the intervention group had the least expensive drug option following the intervention compared to the usual care group.[78] No study reported on access to care.

Intervention Frequency, Delivery Mode, and Number of Components

To examine the effects of intervention frequency, delivery mode, and number of components, we compared the results from one-session interventions, the remotely delivered (no in-person contact) interventions, and the interventions with one or 2 components to the overall data set.

Frequency (one-time compared to pooled total)

Four studies used one-time interventions and 3 of these defined a pooled outcome, goal attainment or non-adherence, as their primary outcome. In general, the results of studies without follow-up visits agreed with the trends seen in the pooled analysis. The 2 studies reporting LDL goal attainment both found better goal attainment in the group receiving pharmacist-led care[48,55] and one of them reported a significant between group difference.[48] Pooled data for dyslipidemia resulted in a non-significant improvement in goal attainment (RR 1.41 [95% CI 0.83, 2.40]). The other outcome was only reported by one study. Murray 2007 found that a one-time pharmacist intervention significantly decreased medication non-adherence.[16] The pooled data followed this trend but did not reach significance (RR 0.72 [95% CI 0.51, 1.08]). Results of the one-time studies did not always have as strong of an effect as seen in the pooled data. However, having only a one-time intervention did not change the direction of effect on goal attainment or non-adherence.

Delivery Mode (remotely delivered compared to pooled data)

Seven studies used a remote intervention, with no in-person contact between pharmacist and patient; 6 of them had goal attainment as their primary outcome. Overall, the results of these

studies were not different than the pooled data. Five of the studies looked at attaining LDL control. The pooled data showed that pharmacist-led care tended to increase attainment of LDL control, although the effect was not significant. Four studies of remote interventions[47,48,55,57] also found greater LDL goal attainment in the intervention groups and 3 of them had a significant result.[47,48,57] The fifth found the groups were similar.[14] A remote intervention seemed to have the same effect as the pooled data, if not more of an impact. Only one study using a remote intervention reported goal attainment for hypertension as its primary outcome.[71] This study had results consistent with the pooled data; the group receiving pharmacist-led care had a larger proportion of patients with blood pressure control.[71] This data suggest that the effect of a pharmacist-led care may be weakened without in-person contact but that pharmacist involvement is still beneficial.

Number of Components (one or 2 component interventions compared to pooled data)

Thirteen studies used interventions with just one or 2 of our 6 defined components. Of these, 4 specified goal attainment or non-adherence as a primary outcome. Three reported goal attainment including one in dyslipidemia, and one in hypertension. Goal attainment for blood pressure was shown in pooled data to be significantly improved by pharmacist-led care (RR 1.38 [95% CI 1.18, 1.62]). The study reporting on blood pressure goal attainment had the same result, significantly better blood pressure control in the intervention group as compared to the control.[63] The pooled data showed a non-significant improvement in lipid goal attainment with pharmacist-led care and the study reporting on dyslipidemia also did not report a significant difference, although the trend was in the same direction.[55] For non-adherence the pooled data showed that pharmacist care led to less non-adherence but the difference was not significant (RR 0.72 [95% CI 0.49, 1.06]). Lee 2006, however, found the proportion of patients' adherent was significantly greater in the intervention group.[77] Having fewer components did not decrease the effect of the pharmacists' interventions on goal attainment or non-adherence.

Quality of Evidence

Strength of evidence for key outcomes is summarized in Table 9.

Table 9. Strength of Evidence[a]

Outcome	Strength of Evidence	Direction	Number of RCTs (N)	Summary
Disease-specific clinical events[b]	Low	Similar	12 (3,355)	Most trials found similar outcomes between pharmacist-led care and usual care. Outcomes were sporadically and inconsistently reported and there were few events. Overall risk of bias was moderate.
Patient satisfaction	Insufficient	Mixed	16 (12,793)	Results were inconsistent for measures of patient satisfaction between pharmacist-led care and usual care. There was variation in how patient satisfaction was reported (scale score or proportions), some measures may not be validated, and some trials used a single item from a multi-item scale. Overall risk of bias was moderate. Given these limitations, conclusions regarding the strength of evidence for patient satisfaction cannot be determined.
Urgent care/ER and hospitalizations	Moderate	Similar	Urgent care/ER 16 (7,166) Hospitalizations 12 (7,455)	Incidence or rates of urgent care/ER visits or hospitalizations were similar between pharmacist-led care and usual care. Overall risk of bias was moderate.
Non-adherence to medications	Low	Similar	17 (5,933)	In most trials medication non-adherence was similar between pharmacist-led care and usual care. Overall risk of bias was moderate. Pooled results from 7 (n=1479) demonstrated a substantial relative reduction but findings were imprecise, not significant, and had substantial heterogeneity (RR 0.58 [95% CI 0.33, 1.01]; I^2 = 82%).
Goal attainment	Moderate	Improved in pharmacist-led care groups	19 (5,816)	Pharmacist-led care improved the proportion of patients achieving guideline recommended laboratory or physiologic treatment goals versus usual care, 51% vs 34% (RR 1.56 [95% CI 1.37, 1.78]; I^2 = 48%). Results were precise and fairly consistent. Cluster RCTs, CCTs, and cohort studies not included in the pooled analysis generally reported improved goal attainment in the pharmacist-led care group. Overall risk of bias was moderate.

[a] Strength of evidence determined for specific outcomes across all chronic disease conditions
[b] *ie,* severe hypoglycemia or hypotension requiring additional interventions

SUMMARY AND DISCUSSION

SUMMARY OF FINDINGS AND STRENGTH OF EVIDENCE

We identified 70 papers (published from 1995 to 2015) representing 62 studies of 64 unique study populations (including 40 RCTs) and enrolling 34,457 patients. Fifty-two of the unique populations studied (81%) were adults with cardiovascular disease, diabetes, dyslipidemia, or hypertension; other conditions included depression, chronic kidney disease, chronic obstructive pulmonary disease, and polypharmacy. Seventeen studies were conducted, at least in part, at VA Medical Centers. Most pharmacist-led interventions were multifaceted, conducted in person, and included multiple contacts between pharmacists and patients. Most studies were not primarily designed to evaluate the effect of pharmacist-led care on clinical or resource use outcomes. Intermediate measures were the most frequently reported outcome with the most common (k=45) being target goal attainment for HbA1c, blood pressure, and cholesterol levels. We included a wide range of studies (randomized controlled trials, controlled trials, interrupted time series, and cohort studies) in order to evaluate a diverse body of literature related to system-level quality improvement projects and pharmacist-led care.

We rated strength of evidence for disease-specific clinical events (low strength of evidence that pharmacist-led care and usual care were similar), patient satisfaction (insufficient evidence), urgent care/emergency department visits and hospitalizations (moderate strength of evidence that pharmacist-led care and usual care were similar), non-adherence to medications (low strength of evidence that pharmacist-led care and usual care were similar), and goal attainment (moderate strength of evidence that pharmacist-led care increased the proportion of patients achieving glycemic, blood pressure, and cholesterol goals compared to usual care). While we did not formally assess strength of evidence on other outcomes we did find that pharmacist-led care was also similar to usual care for depression, health-related quality of life, all-cause mortality, and cost outcomes. However, due to differences in costs reported across studies (program costs, medication costs, visit costs), it is difficult to reach a conclusion about costs. Very few studies reported drug-related problems (inappropriate medication or dosage, drug interactions). Patients in the pharmacist-led care groups generally received a greater number or dose of medications though it was difficult to evaluate whether increased number or dose of medications was an indicator of better care quality.

We identified one additional study that attempted to address the gap in reporting of adverse events.[81] In a post-hoc analysis, the authors achieved a larger sample size by pooling data from 2 similarly conducted RCTs comparing pharmacist-led interventions to usual care for patients with heart failure[16] and hypertension. Adverse drug events and medication errors were secondary outcomes in the original trials. There were 75 events in the intervention groups and 135 events in the control groups. The risk ratio for all events (adverse drug events, preventable adverse drug events, potential adverse drug events, and medication errors) was 0.66 (95% CI 0.50, 0.88) favoring the intervention groups over the control groups. Risk ratios for the individual event categories were similar although not significant for preventable or potential adverse drug events.

Our results concur with findings from other recent systematic reviews. Viswanathan et al, in a review for the Agency for Healthcare Research and Quality (AHRQ), focused on MTM and required interventions to include at least 3 elements: comprehensive medication review, patient-directed education and counseling, and coordination of care.[9] They found low strength of

evidence for a benefit of MTM for health plan expenditures (based on 3 RCTs) although the evidence from non-randomized trials and cohort studies was rated as insufficient strength. There was also a benefit of MTM for hospitalization risk for diabetes (based on one cohort study) but not CHF or COPD (insufficient evidence). There were mixed results for number of hospitalizations with 3 RCTs finding no benefit and one cohort finding a benefit of MTM. Only 5 studies were included in both the AHRQ review and our review. However, both reviews found limited reporting of outcomes such as clinical events, mortality, adverse drug events, and drug-related problems. The authors of the AHRQ review also commented on difficulty interpreting findings as higher values for some outcomes (*eg,* office visits, medication use) may indicate better care for some patients and poorer care for others and many sources of variability are not accounted for in the data analyses.

Another review focused exclusively on blood pressure control in patients with or without diabetes.[82] Included studies were RCTs with interventions delivered by a pharmacist alone or in collaboration with other healthcare professionals. In pooled analyses, pharmacist interventions were associated with reductions in systolic and diastolic blood pressure although heterogeneity was high (I^2=67% for the systolic blood pressure analysis, I^2=83% for the diastolic blood pressure analysis). Subgroup analyses by the type of pharmacist intervention showed greater changes in systolic and diastolic blood pressure with pharmacist-led care compared to collaborative care. No other outcomes were reported.

A 2010 review included studies of interventions, conducted in the US, where the pharmacist was involved in direct patient care (with a "discernable contribution").[83] Outcomes of interest were categorized as therapeutic (*eg,* blood pressure, hospitalizations, mortality, appropriate medication use, eye exams), safety (*eg,* adverse drug events, medication errors), or humanistic (*eg,* patient adherence, patient knowledge, quality of life). The authors reported the percentage of studies reporting an outcome with favorable, non-favorable, mixed, no effect, and unclear findings then performed meta-analyses with data from RCTs if more than 4 RCTs reported the outcome. The therapeutic outcomes eligible for meta-analysis were HbA1c, LDL, and blood pressure. Pooled standard mean difference data favored the pharmacist involvement. Data on adverse drug events (safety outcome) were pooled with an odds ratio favoring the pharmacist involvement (OR 0.53 [95% CI 0.33, 0.83]). Standard mean difference data could also be pooled for 6 humanistic outcomes. Significant differences favoring pharmacist involvement were noted for medication adherence, patient knowledge, and quality of life (general health). Non-significant findings were reported for patient satisfaction and 2 quality of life dimensions – physical functioning and mental health.

APPLICABILITY

The chronic disease conditions addressed in the included studies (cardiovascular disease, chronic kidney disease, COPD, depression, diabetes mellitus, and hypertension) are common among Veterans. Seventeen studies were conducted in VA facilities. The model of pharmacist-led care reported in these studies varied but likely is similar to ongoing programs in VA.

LIMITATIONS AND RESEARCH GAPS/FUTURE RESEARCH

Many of the outcomes reported in this review were not the study-defined primary endpoints and therefore not supported by rigorous research methods or statistical inferences. Among studies included in our review, sample sizes were too small and follow-up periods too short to detect

differences in mortality. There was limited reporting of other clinical events, health-related quality of life, and patient satisfaction. When assessed, authors used varied methods for determining health-related quality of life and patient satisfaction. Scale scores were often not validated, of unknown clinical importance, or included selected findings from subscales. Interventions varied in composition, delivery mode, and intensity as did the usual care comparator, making it difficult to draw conclusions about important intervention characteristics.

One hypothetical benefit of pharmacist-led care for chronic diseases is increased access to care for patients. None of the included studies reported typical measures of access and only 4 studies (2 in patients with depression and one each in patients with hypertension or diabetes) reported patient satisfaction or patient perception measures related to access (*eg,* satisfaction with ability to reach someone in an emergency or satisfaction with availability of advice). Intervention-based increases in the number of scheduled visits or telephone calls may not represent improved access. Further research is needed with conventional measures of access.

A consistent definition of an office visits outcome is needed to distinguish regularly scheduled office visits, study-related office visits, and unplanned office visits. In many cases it was unclear whether the visit was with a pharmacist or primary care provider. Also, a consistently reported cost outcome that includes all of the important economic factors involved in pharmacist-led care would facilitate comparisons across studies and provide more accurate cost-effectiveness estimates.

There was limited reporting of important drug-related problems, in particular drug interactions and inappropriate medications and/or dosages. Some studies did report on adherence with mixed, inconclusive results. Despite existing definitions of polypharmacy, an isolated measure of the number of medications is not an indicator of quality of care as there are situations where adding medications and/or increasing dosages may be helpful. Similarly, de-prescribing medications that emerging evidence suggests are not beneficial and may provide harm may also be helpful. Further research is needed to define and describe these interventions and their association with patient outcomes and value

Finally, the demonstrated improvement in laboratory and physiologic goal attainment due to pharmacist-led care is potentially encouraging. Intervention group pharmacists successfully achieved the intended study objectives. The target goals were based, in part, on recommendations from selected existing clinical practice guidelines and performance measures. The results indicate that future pharmacist-led programs are likely to achieve intended goals. However, there is conflicting evidence that target goals for glycemic, blood pressure, or cholesterol control have long-term beneficial effects on patient outcomes including clinical events, satisfaction, access, hospitalizations, and costs. Therefore, future research needs to carefully assess whether the magnitude of effect on selected intermediate laboratory and physiologic goals translate to improved patient outcomes including clinical events, satisfaction, access, hospitalizations, and costs. Few studies reported differences in potential harms. Thus the available evidence does not answer the question about whether the benefits of pharmacy-led interventions justify potential harms and costs. Ideally, future studies will be designed to fully and accurately address final patient outcomes and cost effectiveness.

CONCLUSIONS

Evidence is limited on the effectiveness and harms of pharmacist-led chronic disease management compared to usual care for clinical outcomes (*ie,* clinical events, all-cause mortality, patient satisfaction, quality of life, and resource utilization). Moderate-strength evidence indicates that pharmacist-led chronic disease management increases goal attainment for HbA1c, blood pressure, and cholesterol levels. Moderate- or low-strength evidence also indicates that pharmacist-led chronic disease management and usual care were similar for urgent care visits or hospitalizations, clinical events, and adherence to medications. Evidence was insufficient for patient satisfaction. There was little reporting of access to care and drug-related problems. These results suggest that future programs are likely to achieve intended laboratory and physiologic goals. However, to accurately assess health care value, future research studies and implementation projects that utilize intermediate laboratory and physiologic goals as measures of effectiveness need to be certain that these goals are clearly linked to improved patient outcomes including clinical events, satisfaction, access, hospitalizations, costs, medication adherence, and drug-related problems without undue harms and costs.

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80. Malone DC, Carter BL, Billups SJ, et al. Can clinical pharmacists affect SF-36 scores in veterans at high risk for medication-related problems? *Med Care.* 2001;39(2):113-122.

81. Murray MD, Ritchey ME, Wu J, Tu W. Effect of a pharmacist on adverse drug events and medication errors in outpatients with cardiovascular disease. *Arch Intern Med.* 2009;169(8):757-763.

82. Santschi V, Chiolero A, Colosimo AL, et al. Improving blood pressure control through pharmacist interventions: A meta-analysis of randomized controlled trials. *J Am Heart Assoc.* 2014;3(2):e000718.

83. Chisholm-Burns MA, Kim Lee J, Spivey CA, et al. US pharmacists' effect as team members on patient care: systematic review and meta-analyses. *Med Care.* 2010;48(10):923-933.

APPENDIX A. SEARCH STRATEGIES

MEDLINE (OVID)

1. Pharmacists/ or pharmacist:.ti,ab.
2. (pharmaceutical care or pharmaceutical services or community pharmac: or clinical pharmac:).ti,ab.
3. 1 or 2
4. Patient care/ or patient care management/
5. Collaborative care.mp. or exp patient care planning/ or intervention:.mp.
6. Case management/ or case management.mp. or care management.mp
7. Disease management/ or disease management.mp. or (disease adj3 prevent:).mp.
8. (chronic disease adj3 management).mp.
9. (chronic disease adj3 prevent:).mp.
10. Chronic care improvement.mp.
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 3 and 11
13. Chronic disease/
14. (chronic adj3 condition:).mp.
15. Exp pulmonary disease, chronic obstructive/
16. Congestive heart failure.mp. or heart failure/ or exp heart failure/
17. Dyslipidemia.mp. or exp dyslipidemia/
18. Diabetes.mp.
19. Hypertension.mp. or exp hypertension/
20. Cancer.mp. or exp neoplasms/
21. Kidney disease.mp. or kidney diseases/ or exp kidney diseases/ or kidney failure.mp.
22. Chronic pain.mp.
23. Depression.mp. or exp depressive disorder/
24. 12 or 14 or 15 or 16 or 18 or 19 or 20 or 21 or 22 or 23
25. Outpatient/ or outpatient:.mp. or outpatient.ti,ab.
26. Ambulatory.mp.
27. Assisted living facilities/ or assisted living.mp.
28. Primary care:.mp.
29. Primary health care/
30. Community pharmac:.mp.
31. Outpatient clinics, hospital/ or clinic.mp.
32. Office visits/ or community health services/ or clinics.mp.
33. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 12 and 24 and 33
35. Limit 34 to (English language and yr=”1995-current”)
36. Limit 35 to “all child (0 to 18 years)”
37. Limit 36 to “all adult (19 plus years)”
38. 36 not 37
39. 35 not 38
40. Limit 39 to (meta analysis or systematic reviews)
41. Limit 39 to (controlled clinical trial or randomized controlled trial)
42. Comparative study/
43. 39 and 42
44. Control group.mp.
45. (control: or compar: or random:).ti,ab.
46. 44 or 45
47. 39 and 46
48. 41 or 43 or 47

CINAHL

1. Pharmacist* OR MH pharmacists
2. (pharmaceutical W1 (care or service?)) OR ((community or clinical) W1 pharmac*) OR collaborative W1 care OR intervention* OR ((care or case) W1 management)
3. Disease N1 management OR disease N3 prevent* OR ((chronic W1 disease) N3 (management or prevent*)) OR chronic W1 care W1 improvement
4. (MH "Case Management") OR (MH "Disease Management")
5. 2 or 3 or 4
6. Chronic N3 condition* OR congestive W1 heart W1 failure OR dyslipidemia OR diabetes OR hypertension OR cancer
7. Kidney N1 disease* OR kidney N1 fail* OR chronic N1 pain OR depression
8. (MH "Kidney Diseases+") OR (MH "Chronic Pain") OR (MH "Depression+")
9. 6 or 7 or 8
10. Outpatient* OR ambulatory OR assisted W1 living OR primary W1 care OR community W1 pharmac* OR clinic?
11. (MH "Outpatients") OR (MH "Ambulatory Care") OR (MH "Ambulatory Care Facilities+") OR (MH "Assisted Living") OR (MH "Primary Health Care") OR (MH "Community Health Centers")
12. 10 or 11
13. 1 and 5
14. (MH "Office Visits")
15. Office W1 visit*
16. 12 or 14 or 15
17. 9 and 13 and 16
18. 9 and 13 and 16 (limiters- randomized controlled trials, Search modes-find all my search terms
19. "meta analysis" OR "systematic review" OR "controlled clinical trial" OR :comparative study" OR "control group" OR control* OR compar* OR random* (limiters-randomized controlled trials, search modes- find all my search terms)
20. (MH "Meta Analysis") OR (MH "Systematic review") OR (MH "Clinical Trials+") OR (MH "Comparative Studies") OR (MH "Control Group")
21. 19 or 20
22. 17 and 21
23. 18 or 22
24. 18 or 22 (limiters- published date: 19950101-20150131; English Language; Exclude MEDLINE records; Human; Age Groups: All Adult, search modes-Find all my search terms)

COCHRANE LIBRARY

1. Pharmacist*
2. Pharmaceutical next (care or service)
3. Collaborative next care
4. Intervention*
5. (care or case) next management
6. Disease near management
7. Disease near prevent*
8. (chronic next disease) near (management or prevent*)
9. Patient care:kw
10. MeSH descriptor: [Chronic Disease] explode all trees
11. MeSH descriptor: [Patient Care Planning] explode all trees
12. #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13. #1 and #12
14. Chronic near condition?
15. Congestive next heart next failure
16. Dyslipidemia or diabetes or hypertension or cancer?
17. Kidney next disease?
18. Kidney next fail*
19. Chronic next pain
20. Depression

21. MeSH descriptor: [heart Failure] explode all trees
22. MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
23. MeSH descriptor: [Dyslipidemias] explode all trees
24. MeSH descriptor: [Diabetes Mellitus] explode all trees
25. MeSH descriptor: [Neoplasms] explode all trees
26. MeSH descriptor [kidney diseases] explode all trees
27. MeSH descriptor: [depressive disorder] explode all trees
28. #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
29. #13 and #28
30. Outpatient? Or ambulatory or clinic?
31. Assisted near living
32. Primary next care
33. Community next pharmac*
34. Primary health care:kw
35. Outpatient clinics, hospital:kw
36. Office visits:kw
37. Community health services:kw
38. #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
39. #29 and #38

    Publication Year from 1995 to 2015

INTERNATIONAL PHARMACEUTICAL ABSTRACTS (IPA)

1. pharmacists/ or pharmacist:.ti,ab.
2. (pharmaceutical care or community pharmacy or clinical pharmac:).ti,ab.
3. 1 or 2
4. patient care/ or patient care management/
5. case management/ or case management.mp. or care management.mp.
6. patient education as topic/ or counsel:.mp.
7. disease management/ or disease management.mp. or (disease adj3 prevent:).mp.
8. medication therapy management/ or (medication adj3 management).mp.
9. (prescription adj3 management).mp.
10. medication optimiz:.mp. or drug interactions/ or therapeutic plan.mp.
11. prescription optimiz:.mp.
12. dt.fs. or drug therapy/ or medication counseling.mp.
13. prescription counseling.mp.
14. drug monitoring/ or prescription monitor:.mp. or drug monitor:.mp.
15. medication surveillance.mp. or medication reconciliation/ or prescription reconciliation.mp.
16. ((medication adj3 review) or (prescription adj3 review) or (drug adj3 review)).mp.
17. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 3 and 17
19. limit 18 to (english language and yr="1995 -Current")
20. limit 19 to journal articles
21. Comparative Study/
22. control group.mp.
23. (control: or compar: or random:).ti,ab.
24. study design.ti,ab.
25. 22 or 23 or 24
26. 20 and 25
27. outpatient/ or outpatient:.mp.
28. ambulatory.mp.
29. urgent care.mp.
30. emergency:.mp.
31. assisted living facilities/ or assisted living.mp.
32. primary care:.mp.
33. community:.mp.
34. 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 26 and 34

APPENDIX B. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Reviewer Comments Export

Pharmacist-led Chronic Disease Management: A Systematic Review of Effectiveness and Harms Compared to Usual Care

Question Text	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	Yes	Thank you
	Yes	
	Yes	
	Yes	
	Yes	
	Yes	
Is there any indication of bias in our synthesis of the evidence?	No	Thank you
	No	
	Yes - only in the Executive Summary	Please see below for our response
	Yes - Description of bias noted in review comments	Please see below for our response
	No	Thank you
	No	
Are there any published or unpublished studies that we may have overlooked?	Yes - Based on your search strategy, I would have thought that a VA study which compared pharmacist-managed ESA clinic (for CKD) would have been included in the section of CKD. References below. (disclosure- I am one of the authors. Having said that, I really don't care if this study is included, if there is good reason why it should not be included.) 1. Aspinall SL, Cunningham FE, Zhao X, Boresi JS, Tonnu-Mihara IQ, Smith KJ, Stone RA, Good CB. Impact of pharmacist-managed erythropoiesis-stimulating agents clinics for non-dialysis chronic kidney disease patients. Am J Kidney Dis 2012; 60 (3): 371-9. PMID 22633556 2. Aspinall SL, Smith KJ, Good CB, Zhao X, Stone RA, Tonnu-Mihara IQ, Cunningham R, for the ESA Clinic Study Group. Incremental cost-effectiveness of pharmacist-managed erythropoietin-stimulating agent clinics for non-dialysis-dependent chronic kidney disease. Appl Health Econ and Health Policy 2013; 11:653-660.	Thank you for identifying this study. We have added the 2 articles to our review.
	No	
	No	
	Yes - Recommendations noted in review comments.	Thank you. Please see below for our response.
	No	
	No	

Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	Three Comments 1) The report mentions in several sections the concern that while attaining many targets better in pharmacy intervention arms, compared to control- those targets have not been shown to improve clinical outcomes, and may actually be associated with harm. I find this somewhat curious- indeed, this is true. But, it is true in hindsight- at the time most of these studies were done, it was generally accepted that these targets were clinically relevant (for instance, that HBA1C of less than 7 was an important target). So, to criticize those intermediate outcomes seems unfair. Indeed, the pharmacists in those studies accomplished what they were asked to accomplish. Today, we would design those studies differently, but we have evidence that came after the referenced studies were done. Furthermore, the fact that most of the studies only demonstrate intermediate outcomes really reflects the roll of the clinical pharmacist in the clinic. Most of the studies were relatively short term, reflecting the reason patients are sent for clinical pharmacist input- usually goal directed (improve blood pressure control, etc). 2. I did not have time to pull individual articles, but I did pull several. Randomly, I looked at the Gattis article. It is published in a reputable journal. In the text, the study is referenced as showing no significant difference in clinical outcomes (overall mortality) but the study reports sig decrease in mortality plus heart failure events. If this outcome was not valid, I feel it should have been clear in the report that while the study reported a clinically relevant improvement in outcome, these were not accepted because of……(In the tables, it shows up under hospitalizations…being significantly less). 3. The review was also intended to evaluate harms. However, "harms" is almost never mentioned throughout the report. Harms are not specifically mentioned in the Executive Summary, and in the individual sections, adverse events are identified as a gap area. However, this is not clearly articulated as seeking evidence for "harms". Suggest explicitly discussing "harms"- which I assume that there is little evidence to address in the review.	1) We have limited our review to the findings of the studies, and rephrased our Limitations and Conclusions 2. The combination outcome from the Gattis article was reported on the Evidence Table in the Appendix but was not carried forward accurately to the report. We have made that change. 3. Although systematic reviews do have different criteria for evidence of harm, there was insufficient evidence on harms as most studies didn't report harms and those that did often didn't report data for the control group.
	The information presented in the report is well constructed and comprehensive in its review of the topic. The research question is concise and well formulated. The summary and analysis of reviewed/considered data upon which an attempted answer to the question is based is objectively and accurately presented. As a reader/reviewer, I was generally able to understand the	Thank you. We have added some examples of "clinical events" in the listing of

distinctions between various measured/evaluated parameters. However, the listing of one or two relevant examples of the authors' "definition" of "clinical events" (within a disease being examined) in relationship to the broader "clinical outcomes" of interest across all disease types (which are explicitly stated) would likely be helpful to future readers and users of the report. That is, what specific thing might qualify as an example of a "clinical event" in the care and treatment of a patient with the specified disease under scrutiny. Most other definitions, measures, and examples are more clearly detailed.	outcomes of interest and as a footnote to the Strength of Evidence tables..
My impression from this systematic review is that pharmacists are not yet good at designing studies and choosing or measuring the outcomes the reviewers deem important. It may be that pharmacist-led team have not been numerous enough or in existence long enough to reach important mortality end points. A more complete description of the evolution of pharmacists from product preparation to patient providers may be helpful. The papers they reviewed were very heterogeneous and not powered to detect the outcomes this review considered most important (e.g. mortality, resource use, access, satisfaction). Nevertheless, they show that pharmacist provided care is for the most part not different from non-pharmacist with goal attainment (LDL, HgbA1c, BP) being better with pharmacist provided care. In the executive summary these facts were presented in a very negative light. For example, on actual page 35, study page 23 paragraph 1 under key findings: they drew conclusions about pharmacist-led care not improving outcomes for depression but specifically stated “studies were not always adequately designed or analyzed for these outcomes”. If that is the case, state lack of study design but do not move to a broader conclusion. My global impression is that this systemic review including categorization, inclusion/exclusion etc. is sound but the way the results are interpreted and the wording of their summary/discussion/conclusion can be improved. The way it is now stated, can be misinterpreted and shed a negative light on what pharmacists have done to date. Specifically, the part on goal attainment which actually showed that pharmacists provided care did better in this category. But, this is undermined by saying that these goals are less strict now anyway and there isn’t a strong evidence that attaining these goals are clinically meaningful. While this may be true, it did not represent the evidence/guidance at the time which is a more global issue. Edits: Actual page 54, study page 41, paragraph 4, line 3: “further study is needed” change to- further studies are needed Actual page 38, study page 26, paragraph 4, line 4: “Two studied	We agree that published studies were not designed to assess mortality and clinical events or authors did not report these findings We would note that most of the included studies looked at the addition of pharmacist-led care to usual care, not pharmacist-led care versus non-pharmacist care. We have rephrased the conclusions about the depression studies. We have modified the wording of the Limitations and Conclusions sections. Edits: Thank you. We have made changes to these sentences.

reported no significant differences" change to- Two studies reported	
The authors have conducted an extensive evidence-based review of Pharmacist-led Chronic Disease Management, particularly as it relates to effectiveness of care. The technical accuracy of the effectiveness of care review meets the evidence-based standards described in the report's methodology. It is noted that the findings of this effectiveness of care review are similar to the 2014 systematic review of outpatient medication therapy management (MTM) interventions conducted by Viswanathan, et. al. (2014 AHRQ review). These similarities would be expected as both analyses used similar evidence-based criteria arriving at a conclusion of difficulty interpreting findings due to heterogeneity of services and interventions. The purpose of this review is to provide the authors, and the Veterans Health Administration, with suggestions and recommendations for improving this ESP review as it pertains to the methodology employed, and implications and applicability of the evidence-based findings contained in this review -First, it would be helpful to the reader to frame the findings of this review in the context of evidence-based reviews of physicians, and other health professionals, chronic disease management services. In its present state, there is no frame of reference or context for understanding the findings of this report. Are these results similar or different than other evidence-based findings of chronic disease management provided by other health care professionals, as well as team-based care? -Second is a critique of the Review of Harms. It is greatly appreciated that the report's Conclusions highlight the importance of achieving patient-specific treatment goals by noting that; 'studies of pharmacist-led care generally achieved intermediate target thresholds designed to achieve a "goal attainment" that should be done cautiously to provide patient-centered high value health care.' This is the essence of comprehensive team-based medication management in an era of accountable health care. However, it is repeatedly stated in the report that, "achieving target goals for HbA1c, blood pressure, and cholesterol reported in the included studies have not been convincingly demonstrated to improve health outcomes but can increase harms and costs." If this statement is to be made, the evidence supporting this finding needs to be presented. The authors will need to summarize the results of other studies in which achieving intermediate target thresholds can cause harms (e.g. A1c < 7% in the elderly, LDL < 70 mg/dl in octogenarians, etc.). In fact, unless additional evidence-based studies describing harms from aggressively achieving intermediate target thresholds can be described, then it is strongly recommended that the report title be corrected to remove the	1) Our findings were based on the available evidence regarding pharmacist-led clinics. Other disease management clinics also frequently use measures such as "goal attainment." We believe we have assessed the most clinically relevant endpoints and initially discussed these with our Technical Expert Panel. There are few studies comparing pharmacist-led chronic disease management to other health care professionals. Thus, we hesitate to draw any conclusions about whether pharmacists provide more or less value. 2) We have modified the Limitations and Conclusions. Regarding harms, please see response above.

word HARMS, because a systematic evidence-based review of harms is not apparent in this analysis.	
-Third, is an inherent bias in the report pertaining to use of an outcome measure without a published taxonomy or official nomenclature. It is understood that the term, "Drug-related Problems" is commonly used in the literature, however there is no published classification system for this term. On the other hand, a published taxonomy of Drug Therapy Problems is available in the National Library of Medicine. One suggestion for improving the report is to utilize the four main published categories of Drug Therapy Problems (e.g. indication, effectiveness, safety, and convenience/adherence) to frame the analysis of drug-related problems. And one other item, on page 14, line 28 there is a statement in regards to the CKD RCT that "drug-related problems were not reported for the control group." Without clarification this may be an irresponsible statement. No human subjects protection program or Institutional Review Board would approve a study in which drug therapy problems were identified in a control group without taking appropriate actions to resolve drug therapy problems in the control group of patients. In Medicine, this would be analogous to identifying a medical condition in a control patient and not doing anything about it.	3) Our list of medication outcomes of interest was approved by our Technical Expert Panel members. We have defined our meaning of "drug-related problems" and removed the term "drug therapy problems" from the review. We have modified the text so the statement about drug-related problems in the control group has been deleted. It would have been more accurate to state that the drug related problems in the control group were not reported in the manuscript.
-Fourth, it is noted that the evaluation approach employed in this analysis is deeply vested in experimental design that dominates the toolkit of evidence-based medicine. This evaluation approach has been summarized by Pawson and Tilley as an, OXO design: observe a system (O), introduce a perturbation/intervention (X) to some participants but not others, and then observe again (O). [1] Pawson and Tilley assert that when studies use the OXO paradigm to evaluate social programs (including most system improvements in medicine), the result is almost always "a heroic failure, promising so much and yet ending up in ironic anticlimax. The underlying logic seems meticulous, clear-headed and militarily precise, and yet findings seem to emerge in a typically non-cumulative, low-impact, prone-to-equivocation sort of way." The usual conclusion and assertion from traditional OXO evaluations of quality-improvement efforts in health care is either that nothing works or that the results are inconsistent and more research is needed. [1] Dr. Don Berwick, former CMS Administrator and champion of the Science of Quality Improvement, has stated that the OXO paradigm most commonly applied in the traditional toolkit of evidence-based medicine is, "a powerful, perhaps unequaled, research design to explore the efficacy of conceptually neat components of clinical practice—tests, drugs, and procedures. For other crucially important learning purposes, however, it serves less well." [2] The introduction of interprofessional and interdisciplinary	4) We evaluated studies that were specifically designed to assess the effectiveness of pharmacist-led chronic disease management. We included many study types including those often used in quality improvement initiatives (as many of these were). We disagree that we held pharmacist-led CDM to "too demanding" quality. Our charge was to conduct a systematic review focusing on the highest quality evidence available, *ie,* controlled clinical trials. Implementation should require evidence of effectiveness that exceeds harms and costs (*ie,* high value). The studies we reviewed did not provide convincing evidence about the value of pharmacist-led care.

	chronic care management systems for establishing a rational medication use system in which pharmacists work with patients to achieve their goals of therapy with zero tolerance for preventable medication harms is a complex, multicomponent intervention—essentially a process of social change. Pawson and Tilley claim that the reason the OXO model fails in this context is because, "experimentalists have pursued too single-mindedly the question of whether a program works at the expense of knowing why it works." [1] The fifth and final area of improvement relates to the implications and applicability of findings within the Veterans Health Administration system. This is to say, that it would be very helpful to address the, "so what question" of the report's findings. In many of the VISN regions of the VA system, there are exemplary pharmacist-led chronic care advances and innovations supported by evidence of improved quality of care. One of the most important topics that is not addressed in this report is reducing pharmacist-led care process variations across the VA VISN's. The science of continuous quality improvement (e.g. statistical process controls, run charts, etc.) provides the tools, techniques and measures to achieve this urgent national need in the care of this country's Veterans. Thank you for the opportunity to serve as an external review for this Evidence-based Report. References: 1.) Pawson R, Tilley N. Realistic Evaluation. London, England: Sage Publications Ltd; 1997. 2.) Berwick DM. The Science of Improvement. JAMA. 2008;299(10):1182-1184. doi:10.1001/jama.299.10.1182.	5) We agree that implications and applicability are important, however, our purpose is to provide a review of evidence for VA policy makers. It is also outside of the scope of this review to address the question of variation in practice across VA VISNs. We highlighted studies conducted in the VA system and are not aware of any other evidence of improved quality of care.
	This is excellent work. My only comment is that I continue to urge the authors to phrase their findings carefully to avoid giving the impression that pharmacist-led care has been shown not to improve outcomes such as mortality. Rather, as the aphorism goes, absence of evidence should not be construed as evidence of absence. That is, the studies have not been done to evaluate those outcomes. This should be made clear.	Thank you. We agree and have reviewed our wording to be clear on the absence of evidence for key outcomes.
	This is a very thorough and well done report. Several comments: 1. Pg. 5, lines 11-12 It is important to clarify these statements to state that in certain patients the more intensive treatment targets may cause harm, but not all patients as the statement reads now. Also, not all patients require less intensive treatment targets. Those recommendations apply to certain high-risk patients (especially in diabetes) whereas this statement implies that all patients would require less intensive targets.	Thank you. 1. We have modified this section.

	2. Pg. 19, Table 3, line 12 The 1 does not have a key corresponding with this and I believe it should be a 'b' instead.	2. We have made the correction
	3. Pg. 23, line 24-25 This statements says there were 3 RCT's but lists 4 references and again in lines 38 & 39 it talks about 2 studies but lists 3 references. Clarification here would be helpful.	3. The 3 RCTs were reported in 4 papers. We have clarified this at the start of the paragraph.
	4. Pg. 28, Figure 6 The placement of this figure is a bit confusing as it is in the middle of the diabetes study discussion but it combines the lipids, hypertension and polypharmacy studies with the diabetes. It may make more sense to put at the end after review of each of those sections.	4. We have placed Figure 6 in the Diabetes section because that is where the first reference to the figure is located. We again refer to Figure 6 in the lipids, hypertension, and polypharmacy sections.
	5. Pg. 29, line 54 The dyslipidemia heading lists 2 RCTs, 2 CCTs, and 2 Cohort studies while the text discusses 7 studies (line 54).	5. We have corrected/clarified the count of studies for the Dyslipidemia section.
	6. Pg. 33, line 14 "in the" is written twice.	6. Thank you, we have made this edit.
	7. Pg. 39, lines 28-31. See comment #1 above as the same applies in this section and also on Pg. 42, lines 21 & 22.	7. We have modified the wording on treatment targets throughout the report.

APPENDIX C. EVIDENCE TABLES

Table 1. Study and Intervention Characteristics – Cardiovascular Disease Studies

Author, year Study design Type of Clinic*	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Cardiovascular Disease or Risk Factors for Cardiovascular Disease							
Taveira 2014[11] RCT Cardio-vascular Risk Reduction Clinic (CRRC) at VAMC	Adults with cardio-vascular disease risk factors 12 months	Inclusion: -actively enrolled in the CRRC clinic (documented CVD or DM) -achieved discharge criteria(HbA1c <7%), BP (DM <140/80 non-DM <140/90), and LDL goals (<2.59 mmol/L)) Exclusion: -conditions that may limit long-term adherence to study visits -life-expectancy < 1 year	Maintenance of cardiovascular risk factor control once it has been obtained Time to failure for guideline goals of HbA1c (failure is >7%) and blood pressure (with DM failure is >140/80 without >140/90) over 12-month study period	Clinical pharmacists who were diabetes core content experts and certified as diabetes educators	1) N=72 -Education -Behavioral and pharmacological interventions -Individualized cardiovascular risk report card -Medications initiated or titrated -Individualized homework and behavior change goals -Coaching of self-care skills *Mode/Frequency:* -Group medical visits (120 minute sessions every 3 months for 1 year; facilitated by pharmacist) plus standard primary care 2) N=73 -Assessed adherence -Titrated medications -Referred to nutrition or physical therapy as needed -Obtained vitals and lab parameters *Mode/Frequency:* -Quarterly CRRC individual clinic visits plus standard primary care (30 minute visit with clinical pharmacist every 2-6 weeks until cardiovascular risk control attained)	N=55 Standard primary care (3-4 visits per year with primary care provider; referrals for nutrition and physical therapy available)	Not reported

Author, year Study design Type of Clinic*	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Irons 2012[12] Cohort (retro) University Cardiol-ogy Group	High cardiac risk patients Patients followed until at goal for several months	Inclusion: -CAD (history of MI, CABG, angioplasty, coronary stent placement, stable angina, evidence of ≥50% stenosis of any major coronary artery, or significant CAD risk equivalent) -baseline SBP >135 mmHg -age 40-85 years -established care with physician from group -≥2 visits with clinical pharmacists (intervention) or cardiologist (control) during study period Exclusion: -history of systolic heart failure (EF < 40%) -significant renal disease -documented non-adherence with appointments (<70% compliance)	Optimize HTN medication management to improve blood pressure control Difference within and between the 2 groups in percentage of patients who obtained BP < 130/80 mmHg during last documented clinic visit within time frame evaluated	Clinical pharmacists	N=59 Collaborative care model; scheduled patient clinic appointments with clinical pharmacists -Adjustment of drug regimens (add, delete, or change HTN medications) -Change dosages of existing HTN medications -Obtain appropriate laboratory measurements -Provide limited physical assessment -Educate referred patients -Follow-up based on adverse events and blood pressure control No specific formulary or algorithms used *Mode/Frequency:* -Minimum of 2 visits with the clinical pharmacist -Initial visit, subsequent follow-up visits were scheduled within 1-4 weeks -If patient was at goal without complications they were scheduled for follow-up in 3 months	N=58 unmatched, met same inclusion criteria; usual care in same cardiology clinic	Cardiologist referred patients to HTN service at his discretion Written collaborative practice agreements in place Consulted for changes of non-hypertensive medications

Author, year Study design Type of Clinic*	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Coronary Artery Disease							
Spence 2014[13] Cohort (retro) Outpatient pharmacy clinical service of integrated health care service	Non-adherent diabetes mellitus or CAD patients with HbA1c or LDL-C outside clinical goals 1 year follow-up	Inclusion: -age ≥18 - pharmacy benefit ≥1 year before and 1 year after index date -included in diabetes or CAD registries - non-adherent (MPR < 0.80) on ≥1 oral medication for diabetes or dyslipidemia -HbA1c ≥8% or LDL-C ≥100 mg/dL Exclusion: -active insulin prescription -resided in skilled nursing facility >10 days or received hospice care during study period -declined consult	Improve medication adherence Primary outcome not stated	Pharmacists who received training on diabetes and dyslipidemia, consultation methodology including motivational interviewing, and workflow training 109 pharmacists participated in OPCS consultations	N=359 with diabetes; N=1,121 with dyslipidemia Outpatient Pharmacy Clinical Service (OPCS); consult (B-SMART methodology) with patients meeting OPCS criteria during prescription pick-up -Identify barriers to medication non-adherence and solutions to these barriers -Motivate patients -Recommend adherence tools -Triage patient if needed to improve medication adherence and outcomes *Mode/Frequency:* -One-time -Face-to-face	N=428 with diabetes; N=1,049 with dyslipidemia matched Usual care; 4 usual care patients matched to each intervention patient by age, gender, and disease (diabetes or dyslipidemia)	Not reported
Olson 2009[14] RCT Non-profit HMO in urban area	Patients with prior coronary artery disease (acute MI, percutane-ous coronary intervention, or coronary artery bypass graft surgery) 2 years	Inclusion: -required only yearly follow-up per CPCRS protocol -≥2 consecutive LDL-C and non-HDL-C values at goal (1 measure within 6 months of enrollment) -controlled blood pressure within 6 months Exclusion: -HbA1c ≥9% in past 6 months -dementia -death within 30 days of randomization -life expectancy <3 years	Maintain lipid control following discharge from cardiac disease management program % of patients maintaining LDL-C goal at study end	Clinical pharmacy specialists	N=214 -Pharmacists telephoned patients to review results of annual fasting lipid profile, blood pressure measurements, and medications and adherence -Counsel on diet and exercise -Make medication adjustments to maintain treatment goals -Order follow-up lab tests -Patients scheduled for follow-ups and notified of results *Mode/Frequency:* -Telephone -Letters informing patients of test results -Scheduled for follow-up fasting lipid profile	N=207 Usual care; fasting lipid profile ordered for 1 year in future; results to be returned to physician who addressed results and ordered follow-up tests as needed; laboratory reminders sent	Intervention patient contacts were documented in EMR for other healthcare providers to review

Author, year Study design Type of Clinic*	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Congestive Heart Failure (CHF)							
Murray 2007[16] RCT University-affiliated inner-city ambula-tory care	Low income patients with CHF 12 months (9 months active intervention, 3 months post-intervention assessment)	Inclusion: -age 50 and older -receive all care (including medications) through same health care system -diagnosis of CHF confirmed by primary care physician -regularly used at least 1 medication for HF -did not use or were not planning to use medication container adherence aid -access to working telephone -hearing in normal range -clinically stable Exclusion: -dementia	Improve adherence to CHF medications, reduce exacerbations requiring ED visits or hospitalizations, improve disease-specific QOL, increase patient satisfaction, reduce health care costs Medication adherence and clinical exacerbations requiring ED visit or hospitalization	Trained by inter-disciplinary team (pharmacist, physician, geriatrician) with guidelines for treating CHF, key concepts in pharmaceu-tical care of older adults, communica-tion techniques, and pharma-cotherapy of drugs for CHF	N=122 -Protocol for intervention based on problem (*eg,* low medication adherence, knowledge) -Baseline medication history assessment of patient knowledge and skills -Patient-centered verbal instruction and written materials about medications (each medication category assigned an icon) -Monitoring of medication use, health care encounters, body weight, other relevant data -Communicated, as needed, with clinic nurses and primary care physicians *Mode/Frequency:* -Baseline interview at enrollment, not with pharmacist -Verbal and written instructions when dispensing medications	N=192 (intentionally randomized more to usual care) Usual care; received prescription services from pharmacists who did not receive specialized training	Information about patients was communicated as needed to clinic nurses and PCPs

Author, year Study design Type of Clinic*	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Gattis 1999(PHARM study)[15] RCT General cardiology faculty clinic	Heart failure (HF) 24 weeks/ median follow-up 6 months	Inclusion: -diagnosis of HF based on signs and symptoms of HF and Left Ventricle EF<45% Exclusion: -life expectancy <6 months -current participant in investigational drug trial -resident of skilled nursing facility -marked dementia or another psychological disorder preventing patient education and follow-up	Optimize HF therapy (including use and dose of ACE inhibitors or alternatives, avoiding digoxin toxicity, avoiding contraindicated drugs or drug interactions, recommending other medication changes) Combined all-cause mortality and heart failure, clinical events	Clinical pharmacist	N=90 -Questionnaire to assess symptoms and response to therapy -Discussed patient's case and verbally provided therapeutic recommendations regarding optimization of therapy to attending physician -Recommendations based off patient interview, history, and current drug regimen -Discussed changes in drug therapy with patient (purpose of each drug, importance of adherence) -Provided written information on directions for use and potential adverse events -Provided patients with telephone number to contact if questions or problems -Telephone follow-up at 2, 12, and 24 weeks with instruction to contact physician if continued or worsening symptoms (pharmacist also contacted physician to discuss these cases) *Mode/Frequency:* -Telephone follow after initial clinic visit -Written information on medication -Provided telephone number to contact if questions or problems -Clinical pharmacist discussed changes made in drug therapy with the patient	N=91 Usual care (no pharmacist recommenda-tions or patient education; physician and/or physician assistant/nurse practitioner did patient assessment and education) -Pharmacist contacted patients at 12 and 24 weeks to identify clinical events	Attending physician, nurses, social workers, dietitians -Discussed patient's case and verbally provided therapeutic recommendations regarding optimization of therapy to attending physician

*Record whether primary care or specialty, if academic affiliated, if rural or urban

CHF = congestive heart failure; CPCRS = Clinical Pharmacy Cardiac Risk Service; ED = emergency department; EMR = electronic medical record; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; EF = ejection fraction; HDL-C = high-density lipoprotein cholesterol; QOL = quality of life; TSH = thyroid-stimulating hormone; CAD=coronary artery disease; HTN=hypertension; HbA1c=glycosylated hemoglobin; ACE=angiotensin converting enzyme; BP=blood pressure; ESRD=end stage renal disease; DRP=drug related problem

Table 2. Drug-related Problems Outcomes – Cardiovascular Disease Studies

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse event % (n/N)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Cardiovascular Disease or Risk Factors for Cardiovascular Disease										
No studies reporting										
Coronary Artery Disease										
Spence 2014[13] IG=1,121 CG=1,049	NR	NR	NR	NR	NR	NR	Adherence at 1 year *MPR* 0.70 *% adherent* 37 (419/1121)	*MPR* 0.74 (P=.003 vs pharm) *% adherent* 38 (403/1049) (P=.62 vs pharm)	NR	NR
Olson 2009[14] IG=214 CG=207	NR	NR	NR	NR	NR	NR	Persistence with lipid-lowering therapy 86.5%	85.5% (P=.78)	Coronary Event 3.3%	5.8% (P=.21)
Congestive Heart Failure										
Gattis 1999[15] IG=90 CG=91	Fraction of target ACE inhibitor dose[a] 1.0 (0.5, 1.0)	0.5 (0.19, 1) (P<.001)	NR	NR	NR	NR	NR	NR	NR	NR
Murray 2007[16] IG=122 CG=192	NR	NR	NR	NR	NR	NR	"Taking adherence" during intervention 79% (71% at follow-up) "Scheduling adherence" during intervention 53% (49% at follow-up) "Refill adherence" during study period 109%	68% (67% during follow-up) 47% (49% during follow-up) 105% P=.007	Adverse event or medication error 38% (42/112)	47% (91/192) (P=.11)

[a] Median (25^{th}, 75^{th} percentiles)

CG = control group; IG = intervention group; MPR = medication possession ratio; NR = not reported

Table 3. Mortality, Quality of Life, Access, and Patient Satisfaction Outcomes – Cardiovascular Disease Studies

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Cardiovascular Disease or Risk Factors for Cardiovascular Disease								
No studies reporting								
Coronary Artery Disease								
Olson 2009[14] IG=214 CG=207	8.4%	7.7% (P=.80)	NR	NR	NR	NR	NR	NR
Congestive Heart Failure								
Gattis 1999[15] IG=90 CG=91	3% (3/90)[a]	5% (5/91)[a] OR 0.59 (95% CI 0.12, 2.49) (P=.48)	NR	NR	NR	NR	NR	NR
Murray 2007[16] IG=122 CG=192	NR	NR	Disease specific, improvement from baseline 6 months: 0.28 12 months: 0.39	6 months: 0.21 (P=.52) 12 months: 0.24 (P=.21)	NR	NR	Satisfaction with pharmacy services, improvement from baseline to 12 months: 1.0	0.7 (P=.02)

[a] Primary outcome was all-cause mortality and nonfatal heart failure; OR 0.22 (95% CI 0.06, 0.63); P=.005
CG = control group; IG = intervention group

Table 4. Healthcare Utilization and Cost Outcomes – Cardiovascular Disease Studies

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Cardiovascular Disease or Risk Factors for Cardiovascular Disease										
Taveira 2014[11] IG=73 Individual IG=72 Group CG=55	Mean # of PCP visits[a] (SD) Individual: 2.8 (1.1) Group: 3.0 (1.2)	2.8 (1.0) (P=.46 overall)	Mean # of visits[a] Individual: 0.4 (0.8) Group: 0.6 (1.0)	0.6 (1.1) (P=.35)	Mean # of visits[a] Individual: 0.3 (0.7) Group: 0.4 (0.8)	0.2 (0.5) (P=.18 overall)	Individual: no change in cholesterol (0.9 to 1.1), BP (2.3 to 2.4), or antihyper-glycemic meds (1.9 to 1.9) from baseline Group: increase in BP (2.1 to 2.3) and antihyper-glycemic meds (1.7 to 1.8) from baseline (P<.05)	Decrease in cholesterol (1.3 to 1.2) and antihyper-glycemic meds (1.9 to 1.8) from baseline (P<.05)	NR	NR
Irons 2012[12] IG=59 CG=58	Clinic visits or BP assessment (outside of scheduled appointments) per year of follow-up 10.7 (9.52, 12.09)	3.45 (3.01, 4.12) P<.0001	NR	NR	NR	NR	Number of anti-hypertensive agents (median) 3.0 (3.0, 4.0)	2.0 (2.0, 3.0) P=.0001	NR	NR
Coronary Artery Disease										
Spence 2014[13] IG=1,121 CAD CG=1,049 CAD	NR	NR	1-year follow-up 4.6% (51/1121)	4.5% (47/1049) (P=.94 vs pharm)	1-year follow-up 1.3% (15/1121)	2.1% (22/1049) (P=.17 vs pharm)	NR	NR	Cost savings (system)[b] $11,640,296 Cost of program: $1,713,468 Approximately $5.79 saved for every $1 spent on program	NR

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Olson 2009[14] IG=214 CG=207	NR	NR	NR	NR	33.6%	27.1% (P=.14)	NR	NR	NR	NR
Congestive Heart Failure										
Gattis 1999[15] IG=90 CG=91	NR	NR	NR	NR	Re-admission rate 29%	Re-admission rate 42% P=.03	Receiving ACE inhibitor at follow-up 87% (78/90) Receiving ACE alternative 75% (9/12)	79% (72/91) (P=.18) 26% (5/19) (P=.02)	NR	NR
Murray 2007[16] IG=122 CG=192	NR	NR	All-cause 2.2 (3.3) Heart failure 0.3 (1.0)	2.7 (4.9) IRR 0.82 (0.70, 0.95) 0.3 (1.3) IRR 1.09 (0.42, 2.87)	All cause 0.8 (1.7) Heart failure 0.1 (0.5)	1.0 (1.8) IRR 0.81 (0.64, 1.04) 0.2 (0.6) IRR 0.77 (0.28, 2.10)	NR	NR	Total outpatient costs (mean) $5483 (SD $6434) Total inpatient costs (mean) $5550 (SD $13847)	$6373 (SD $6501) $7827 (SD $20413)

[a] Results are for patients with diabetes only (n=178 of 200 patients enrolled)
[b] From reduced ER visits and hospitalizations for DM and CAD patients
CG = control group; IG = intervention group

Table 5. Goal Attainment Outcomes – Cardiovascular Disease Studies

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal (n/N)	
		Pharmacy component	Control
Cardiovascular Disease or Risk Factors for Cardiovascular Disease			
Taveira 2014[11] IG=73 Individual IG=72 Group CG=55	Maintenance of HbA1c ≤ 7%, BP ≤140/80 mmHg, LDL cholesterol ≤ 2.59 mmol/l	**HbA1c failure rates per quarter[a] (95% CI)** Individual: 0.24 (0.18, 0.33) (/156 person-quarters) Adj HR (vs control) 0.34 (0.21, 0.53) Group: 0.36 (0.28, 0.47) (/129 person-quarters) P=.07 to individual Adj HR (vs control) 0.49 (0.32, 0.75) **BP failure rates per quarter[a]** Individual: 0.22 (0.16, 0.30) (/166 person-quarters) Adj HR (vs control) 0.43 (0.27, 0.68) Group: 0.31 (0.23, 0.41) (/140 person-quarters) Adj HR (vs control) 0.62 (0.41, 0.95) **LDL guideline adherent[a]** Individual: 75.0% Group: 88.5%	**HbA1c:** 0.82 (0.69, 0.96) (/60 person-quarters) (P<.001 compared to intervention) **BP:** 0.53 (0.40, 0.71) (/87 person-quarters) (P<.002) **LDL adherent:** 84.3% (P=.12)
Irons 2012[12] IG=59 CG=58	Blood pressure < 130/80 mmHg (Note: goal was not specified for the control group)	49% (29/59)	31% (18/58) (P=.0456)
Coronary Artery Disease			
Olson 2009[14] IG=214 CG=207	LDL < 100 mg/dL non-HDL <130 mg/dL diabetes, multi-vessel coronary disease, at least 1 recurrent coronary event, or current smoker had LDL goal < 70 mg/dL non-HDL goal <100 mg/dL Blood pressure < 140/90 mmHg diabetes or chronic kidney disease had goal < 130/80 mmHg	LDL < 100 mg/dL: 91.0% LDL < 70 mg/dL: 68.6% Non-HDL-C 88.7% BP < 140/90 mmHg: 75.0% BP < 130/80 mmHg: 60.0%	LDL < 100 mg/dL: 93.1% (P=.46) LDL < 70 mg/dL: 56.8% (P=.23) Non-HDL-C 88.2% (P=.89) BP < 140/90 mmHg: 84.2% (P=.03) BP < 130/80 mmHg: 54.5% (P=.71)
Congestive Heart Failure			
No studies reporting			

[a] Results are for patients with diabetes only (n=178 of 200 patients enrolled); results for patients without diabetes (n=22) were described narratively due to small number of patients per group

CG = control group; IG = intervention group

Table 6. Study and Intervention Characteristics – Chronic Kidney Disease Studies

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Cooney 2015[20] RCT CBOCs within Cleveland VA	Patients with CKD Study period was 1 year; patients were called before appointment and after (with lab results, etc.)	Inclusion: -moderate to severe CKD (eGFR<45) -GFR<60 between 90 days and 2 years prior -≥1 primary care visit in year prior to study Exclusion: -ESRD -ever referred for hospice care -<18 or >85 years old	Improve CKD care Last clinical systolic BP for patients with poorly controlled HTN at baseline	Clinical pharmacists with ability to order and review labs and prescribe medications	N=1070 -Delivery system redesign: a. engaging pharmacists to interact with patients and collaborate electronically with PCPs b. self-management support for patients (informational pamphlet) c. CKD registry to identify patients with CKD not receiving guideline adherent care, for decision support during phone call, and to facilitate documentation of intervention -Phone contact prior to appointment to discuss CKD, HTN -Reviewed medications and lifestyle modifications, ordered recommended labs, arranged nephrology consults if severe CKD -Called patients to review abnormal results and initiate appropriate non-HTN medication changes -Recommended HTN management tactics to PCPs *Mode/Frequency:* -Phone-based, 2 calls	N=1129 Usual care from PCPs	Recommendations for HTN management given to PCPs in progress notes

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Aspinall 2012/2013[21,22] Historical cohort 16 VA Medical Centers	Receiving ESAs for NDD-CKD 6 month follow-up	Inclusion: -50 randomly selected outpatients from each site -NDD-CKD defined as eGFR<60 mL/min/1.73m^2 -receiving ESA on long-term basis	Compare quality of ESA prescribing and monitoring with and without pharmacist-managed clinics Quality of ESA prescribing, (*ie,* proportion of hemoglobin values within 10-12g/dL)	Pharmacists with scope of practice that allowed them to dose and monitor ESA therapy	N=314 (10 clinics) NOTE: an additional 91 patients categorized as receiving usual care at ESA clinic sites -Independently dose and monitor ESAs (guidelines in place) *Mode/Frequency:* Not reported	N=167 (6 clinics) -Usual care (physician-based)	None reported
Pai 2009[18] Pai 2009[17] RCT (pilot) Non-profit university-affiliated dialysis clinic	ESRD patients 2 years	Inclusion: -English speaking ->18 years old -stable hemodialysis regimen for ≥3 months	Effect of pharmaceutical care on DRPs, drug use, drug costs, hospitalizations Primary: change in quality of life (Renal Quality of Life Profile – RQLP)	Nephrology-trained clinical pharmacist or pharmacists completing post-doctoral training in nephrology pharmacotherapy	N=57 (30/57 [53%] did not complete study) -One-on-one in-depth drug therapy review conducted by clinical pharmacist -At meetings approximately every 8 weeks: -patient interview -generate drug therapy profile -identify and address DRPs -provide health care provider and patient education -review labs *Mode/Frequency:* -In clinic, one-on-one -Every 8 weeks during the 2 year study period	N=47 (21/47 [45%] did not complete study) Usual care (brief drug therapy reviews by dialysis nursing staff as mandated by clinic policy)	Physician, fellow, nurse, social worker, dietitian involved in monthly formal patient reviews -pharmacist gave provider education

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Bucaloiu 2007[19] Retro cohort Nephrol-ogy clinic	Anemia of CKD Minimum of 6 months; maximum of 1 year	Inclusion: -adults -anemia of CKD -treated with outpatient EPO -followed for ≥6 months Exclusion: -managed by hematology-oncology or another nephrology group -on dialysis	Clinical and economic benefits Primary outcome not specified	NR	N=62 Protocol-driven pharmacist-managed program to manage anemia of CKD Received epoetin alfa and sucrose intravenously per protocol *Mode/Frequency:* -Patients followed between 6 months and 1 year -Hemoglobin/iron saturation measured at least monthly	N=74 matched Managed by PCPs (no protocol or pharmacist oversight) Received epoetin alfa	NR

CG = control group; CKD = chronic kidney disease; DRP = drug-related problem; EPO = epoetin alfa; ESA = erythropoiesis-stimulating agents; ESRD=end stage renal disease; HTN = hypertension; IG = intervention group; NDD = non-dialysis-dependent; NR = not reported; PCP = primary care physician

Table 7. Drug-related Problems Outcomes – Chronic Kidney Disease Studies

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Cooney 2015[20] IG=1,070 CG=1,129	NR	NR	NR	NR	NR	NR	Medication Adherence 6.8 (1.2)	6.7 (1.2) P=.70	NR	NR
Aspinall 2012/2013[21,22] IG=314 CG=67 (Additional 91 patients receiving usual care at ESA clinic)	NR	NR	NR	NR	NR	NR	NR	NR	Thrombo-embolism[a] n=6 (0.02/180 pt-days) Heart Failure[b] n=18 (0.06/180 pt-days) Uncon-trolled HTN[c] n=185 (0.66/180 pt-days)	Thrombo-embolism n=7 (0.05/180 pt-days) Heart Failure n=9 (0.06/180 pt-days) HTN n=73 (0.48/180 pt-days) All "clinically similar"
Pai 2009[18] IG=57 CG=47	*Sub-therapeutic dosage:* 14% of 530 DRPs identified *Untreated indication:* 25%	NR	NR	NR	NR	NR	NR	NR	*Overdose:* 5% of 530 DRPs identified	NR
Bucaloiu 2007[19] IG=62 CG=74	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

CG = control group; DRP = drug-related problem; HTN = hypertension; IG = intervention group; pt-days = patient days

[a] Thromboembolic event (myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism) resulting in an emergency department visit or hospitalization

[b] Resulting in an emergency department visit or hospitalization

[c] Systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg

Table 8. Mortality, Quality of Life, Access, and Patient Satisfaction Outcomes – Chronic Kidney Disease Studies

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)		Other Outcomes
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	
Cooney 2015[20] IG=1,070 CG=1,129	50/1070 4.7%	74/1129 6.6% P=.06	No sig diff between intervention and control for SF12MCS, SF12PCS, KDQOL Burden, KDQOL Effects		NR	NR	92% of participants surveyed felt pharmacists provided useful information and would recommend program to others	NR	NR
Pai 2009[17,18] IG=57 CG=47	15/57 26%	12/47 26%	Total RQLP Baseline: 71.9 (40) 1 year 71.4 (33.6) 2 years 56.5 (32.6)	Baseline: 74.5 (33.5) 1 year ES 0.08 87.5 (30.4)[a] ES 0.53 2 years 68.8 (35.8) ES 0.34	NR	NR	NR	NR	NR

[a] P<.05 vs pharmacist intervention

CG = control group; ES = effect size; IG = intervention group; KDQOL = Kidney Disease Quality of Life; NR = not reported; RQLP = renal quality of life profile (higher score = worsening quality of life); SF12 = Short Form; MCS = mental component score; PCS = physical component score

Table 9. Healthcare Utilization and Cost Outcomes – Chronic Kidney Disease Studies

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Cooney 2015[20] IG=1,070 CG=1,129	NR	NR	NR	NR	NR	NR	Classes of antihypertensives: P=.02 (subjects in IG prescribed more classes of anti-HTN meds)		ESRD 26/1070 (2.4%)	ESRD 20/1129 (1.8%) P=.28
Aspinall 2012/2013[21,22] IG=314 CG=67 (Additional 91 patients receiving usual care at ESA clinic)	NR	NR	NR	NR	NR	NR	Medication adjustment based on hemoglobin[a] Increased 176/305 (57.7%) Withheld or Decreased 80/131 (61.1%)	Increased 30/105 (28.6%) (P=.009) Withheld or Decreased 37/108 (34.3%) (P=.09)	Cost[b] $13,412 QALYs 2.096	Cost $16,173 QALYs 2.093
Pai 2009[18] IG=57 CG=47	NR	NR	NR	NR	Significantly (P=.02) fewer all-cause hospitalizations in intervention group (overall 42% fewer hospitalizations in intervention group)		Mean number of drugs significantly (P<.05) lower in intervention group at each medication review (overall 14% fewer drugs in intervention group)		Mean drug costs were lower among patients in intervention group; difference significant (P<.05) only at 3rd drug therapy review (overall $6 less in intervention group)	
Bucaloiu 2007[19] IG=62 CG=74	NR	NR	NR	NR	NR	NR	Weekly dose of EPO 6,698 units	12,000 units (P=.001)	Estimated annual cost savings per patient $3,860	

CG = control group; EPO = epoetin alfa; ESA = erythropoiesis-stimulating agents; IG = intervention group; NR = not reported; QALYs = quality-adjusted life years

[a] Proportion of hemoglobin *tests* resulting in change in ESA dose

[b] Modeled over 5 years

Table 10. Goal Attainment Outcomes – Chronic Kidney Disease Studies

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal (n/N)	
		Pharmacy component	Control
Cooney 2015[20] IG=1,070 CG=1,129	BP Control <130/80mmHg	185/441 (42.0%)[a]	177/429 (41.2%)[a] (P=.84)
Aspinall 2012/2013[21,22] IG=314 CG=67 (Additional 91 patients receiving usual care at ESA clinic)	Hemoglobin 10-12g/dL	Proportion of *values* within range 1284/1807 (71.1%)	Proportion of *values* within range 345/606 (56.9%) (P<.001)
Bucaloiu 2007[19] IG=62 CG=74	Hemoglobin in goal range (11-12.9 mg/dL) Average iron saturation (T-sat) in goal range (20%-50%)	69.8% of measured values 64.8% of measured values	43.9% of measured values (P=.0001) 40.4% of measured values (P=.043)

BP = blood pressure; CG = control group; IG = intervention group; NR = not reported

[a] Denominators are patients with BP > 130/80mmHg at baseline

Table 11. Study and Intervention Characteristics – Chronic Obstructive Pulmonary Disease Studies

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Solomon 1998[23] Gourley 1998[24] RCT 10 VA Medical Centers; 1 University Hospital (8 sites participate in COPD trial)	Patients with COPD 6 months	Inclusion: -ambulatory COPD patient -pulmonary function tests for diagnosis -currently treated for COPD (≥1 inhaler) -capable of using inhaler -read & write English -≥40 years old -access to telephone Exclusion: -history of severe/life-threatening COPD -life-expectancy < 6 months -hospitalized or ED visit past 2 weeks -lung infection past 2 weeks -CHF class III or IV -other lung disease except asthma -alcohol or drug abuse -investigational drug trial within past 30 days	Improve compliance, patient satisfaction, knowledge, and quality of life Patient knowledge, medication compliance, health resource use	Clinical pharmacists	N=43 Standardized patient assessment and a series of regularly scheduled therapeutic and educational interventions designed for optimal disease management -Implement care plan -Educate patients -Counsel patients -Patient assessment and follow-up Focused on management of COPD patients relative to: -Symptom control -Patient compliance -Drug product selection -Use of resources -Patient satisfaction with care -Disease and disease management -Knowledge -Quality of life *Mode/Frequency:* -6-month treatment period with scheduled visits for treatment patients at enrollment and then at one-month intervals (4-6 wks) for a total of 5 visits -Telephone follow-up	N=55 Usual care (no supplemental education or assessment of needs beyond what was customarily offered at each site)	Collaborate with physicians to implement a patient-specific, optimized, step-care approach

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ED = emergency department

Table 12. Drug-related Problems Outcomes – Chronic Obstructive Pulmonary Disease Studies

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Solomon 1998 Gourley 1998[23,24] IG=43 CG=55	Drug needed not prescribed 4.5% (15/336 problems identified by pharmacists) Drug not needed but prescribed 1.5% (5/336) Dose problem 1.2% (4/336)	NR	NR	NR	Risk of interaction 8.9% (30/336 problems identified by pharmacists)	NR	NR	NR	NR	NR

CG = control group; IG = intervention group; NR = not reported

Table 13. Mortality, Quality of Life, Access, and Patient Satisfaction Outcomes – Chronic Obstructive Pulmonary Disease Studies

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Solomon 1998 Gourley 1998[23,24] IG=43 CG=55	NR	NR	Global Symptom Assessment[a] Baseline: 3.4 (1.1) 6 months: 3.2 (1.2) Quality of Life[b] (8 items) No significant changes from baseline; no differences from control group	Baseline: 3.4 (1.3) 6 months: 3.3 (1.5) Significant worsening of "bodily pain" dimension from baseline to 6 months (P=.03)	NR	NR	PCQ – 10 items Intervention group patients had more favorable response to pharmacist than control for all 10 items; differences were significant (P<.05) for 7 of 10 items	

[a] Patient rating of overall status with respect to control of COPD: 0 = no symptoms present, 5 = symptoms so severe that one could not perform normal daily activities
[b] Health Status Questionnaire 2.0
CG = control group; IG = intervention group; NR = not reported; PCQ = Pharmaceutical Care Questionnaire (developed for the study and addressing technical-professional competency, patient knowledge, and interpersonal relationship)

Table 14. Healthcare Utilization and Cost Outcomes – Chronic Obstructive Pulmonary Disease Studies

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Solomon 1998 Gourley 1998[23,24] IG=43 CG=55	Mean (std) 0.81 (0.93)[a]	1.17 (1.03) (P<.05)	Mean (std) 0.15 (0.36)[a]	0.17 (0.48) (P=NS)	Mean (std) 0.10 (0.37)[a]	0.13 (0.34) (P=NS)	New medications[a] Mean (std) 0.51 (0.93)	0.36 (0.71)	NR	NR

[a] At 6 month follow-up

CG = control group; IG = intervention group; NR = not reported; NS = not statistically significant

Table 15. Goal Attainment Outcomes – Chronic Obstructive Pulmonary Disease Studies

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal (n/N)	
		Pharmacy component	Control
No studies reporting			

Table 16. Study and Intervention Characteristics – Depression Studies

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Adler, 2004[25] RCT Primary care clinics: 5 academic, 2 suburban, and 1 urban	Positive screen for depression or dysthymia 6 months	Inclusion: -met DSM-IV diagnostic criteria for major depressive disorder and dysthymia -no terminal illness, pregnancy, alcoholism, bipolar or psychotic disorder -English language literate -age ≥18 -patient consent	Increase antidepressant (AD) use AD use & changes in severity of depression as measured by a modified Beck Depression Inventory (mBDI)	Experienced clinical pharmacists with PharmD	N=258 -Medication history -Assess drug-related problems -Monitor drug efficacy & toxicity -Patient education & encouragement -Communicate findings to primary care provider -General social support, help overcoming system inadequacies, encourages patients, facilitates referrals *Mode/Frequency:* -At least 9 contacts in18 months -Initial contact by telephone to set up appointment	N=249 Standard Primary care physician (PCP) care	Information sharing with PCP
Capoccia, 2004[26] Boudreau, 2002[27] RCT University urban family practice	Referred to study after a new DSM-IV diagnosis of depression & Rx for AD 12 months	Inclusion: -no terminal illness, substance abuse, psychosis, pregnancy, suicide attempt; -English language -age ≥18 -patient consent	Improve outcomes Reduction in depression as measured by no longer meeting diagnostic criteria and improvement in symptom checklist (SCL-20)	Experienced staff clinical pharmacist and PharmD resident	N=41 -As many as 13 follow-up telephone calls to assess symptoms, concerns, and side effects; titrate doses; discontinue or change medication; manage Ads; patient education & motivation -Facilitated appointments with mental health -Additional therapy for other issues (*ie* sexual dysfunction/insomnia) -Provide support *Mode/Frequency:* -Weekly calls first 4 weeks, every 2 weeks through week 12, every other month from 4-12 months -Subjects encourage to visit PCP at weeks 4 and 12	N=33 Usual care (encouraged to use available resources which included pharmacists)	Primary care & psychiatrist case review with physicians

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Finley, 2003[28] RCT Urban primary care clinics of HMO	Primary care initiation of AD 6 months	Exclusion: -AD used in prior 6 months -concurrent psychiatric or psychological treatment -mania or bipolar disorder -psychotic symptoms -eminent suicidality -substance abuse or dependence -psychiatric treatment indicated	Improve drug adherence, patient outcomes, provider and patient satisfaction, and medical resource utilization Antidepressant adherence measured as medication possession ratio (MPR) & continued antidepressant between 3-6 months	Experienced clinical pharmacists with PharmD	N=75 -Intake interview: drug, medical, & psychiatric history; contraindications -Patient education: use of ADs, treatment options -Titration of ADs -Prescribe ancillary medications -Recommend changes in ADs -Follow-up for adherence, drug benefits and side effects, other social factors -Assess severity of condition -Identified stressors, other key factors *Mode/Frequency:* -Intake interview -5 follow-up contacts by phone and 2 clinic visits & on-call	N=50 Usual care - brief counseling on the prescribed drug, therapeutic end points, and side effects	Psychiatrist mentor met with clinical pharms to discuss and update on patients and consult Approval needed from PCP to change drug
Finley, 2002[29] Non-randomized comparison group; pilot study Urban primary care clinics of HMO	Primary care initiation of AD 6 months	Inclusion: -identified by PCP as suffering from depression -received prescription for AD medication Exclusion: -AD use past 6 months -under care of psychiatrist in HMO -imminent suicidality -psychotic symptoms -active substance abuse/dependence -history of manic episodes	Increase medication adherence and patient satisfaction Medication adherence rates, patient satisfaction, and resource utilization patterns	Experienced clinical pharmacists with PharmD and psychiatric experience	N=91 -Intake interview including: medication, medical, social, and mental health history; symptoms; and environmental stressors -Patient education including disease information, use of ADs, treatment options, importance of adherence, and potential adverse effects -Pharmacists could prescribe ancillary medications and recommend changes in ADs *Mode/Frequency:* -Intake interview -5 follow-up contacts by phone and 2 clinic visits & on-call	N=129 unmatched Usual care (treated by PCP)	Psychiatrist mentor, recommended medication changes to PCP

AD = antidepressant medication; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; HMO = health maintenance organization; mBDI = modified Beck Depression Inventory; MPR = medication possession ratio; PCP = primary care provider; PharmD = Doctor of Pharmacy; RCT = randomized controlled trial; Rx = prescription; SCL-20 = Symptom Checklist Depression Scale

Table 17. Drug-related Problems Outcomes – Depression Studies

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/ adverse events % (n/N)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Capoccia 2004[26] IG=41 CG=33 3 outcome assessments over 12 months; extracted 12 month data	NR	NR	NR	NR	NR	NR	12 months Patient reported use <25 of last 30 days 41%	Patient reported use <25 of last 30 days 43%	NR	NR
Finley 2003[28] IG=75 CG=50	NR	NR	NR	NR	NR	NR	3 month compliance 76%; MPR 0..92 6 month compliance 67%; MPR 0.83	3 month compliance 60%; MPR 0.89 (P=.48) 6 month compliance 48%; MPR 0.77 (P=.26)	NR	NR
Finley 2002[29] IG=91 CG=129	NR	NR	NR	NR	NR	NR	6 month MPR 0.81 Use of ADs after 3 months 76%	6 month MPR 0.66 (P<.005) Use of ADs after 3 months 51% (P=.001)	NR	NR

AD = antidepressant medication; CG = control group; IG = intervention group; m=months; MPR = medication possession ratio; NR = not reported

Table 18. Mortality, Quality of Life, Access, and Patient Satisfaction Outcomes – Depression Studies

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)		Depression	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Adler 2004[25] IG=258 CG=249	NR	NR	SF-12 Mental component (MCS) 40.4 Physical Component (PCS) 42.9	MCS 38.6 (P=.19) PCS 42.9 (P=NS)	NR	NR	"Based on exit interviews patients expressed high satisfaction with the pharmacist intervention"		NR	NR
Capoccia 2004[26] IG=41 CG=33 3 outcome assessments over 12 months; extracted 12 month data	NR	NR	Mean SLC-20 NS difference (P=.92) Mean SF-12 mental NS difference (P=.46) Mean SF-12 physical NS difference (P=.18)		NR	NR	Good or excellent quality of care (12 months): 80% No overall difference in satisfaction with depression care (P=.19) or overall healthcare (P=.48) between groups	Good or excellent quality of care: 77%	Diagnosis of major depression: Groups similar (P=.32) at 12 months at least 50% decrease in SCL-20: 72%	at 12 months at least 50% decrease in SCL-20: 80% (P=.39)

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)		Depression	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Finley 2003[28] IG=75 CG=50	NR	NR	56% reduction in WSDS (n=54)	67% reduction in WSDS (n=24) (P=.36)	Mean of one 5-point question about availability of advice (higher= more satisfied) 4.3 (n=59)	3.8 (n=33) (P<.05)	Mean of one 5-point question about treatment of depression, (higher= more satisfied) 4.2 (n=59) Significantly more satisfied with 6 out of 11 aspects of care (P<.05)	3.8 (n=33) Students t-test: P=.06 X^2 test paired data: P=.066 Wilcoxon score: P=.023	41% with 50% reduction in BIDS Percent achieving remission (BIDS score <9) 55.6% (n=54)	54% with 50% reduction in BIDS (P=.27) 58.3% (n=24) (P=.36)
Finley 2002[29] IG=91 CG=129	NR	NR	NR	NR	Mean of one 5-point question about availability of advice (higher= more satisfied) 4.3 (n=56)	3.7 (n=55) (P=.003)	Mean of one 5-point question about treatment of depression, (higher= more satisfied) 3.9 (n=56)	4.0 (n=59) (P=.581)	NR	NR

AD = antidepressant medication; BIDS = Brief Inventory for Depressive Symptoms; CG = control group; IG = intervention group; NR = not reported; NS = not significant; SCL = symptom check list; SF-12 = Medical Outcomes Study Short Form 12; WSDS= Work and Social Disability Scale

Table 19. Healthcare Utilization and Cost Outcomes – Depression Studies

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Adler 2004[25] IG=258 CG=249	NR	NR	NR	NR	NR	NR	Patient on ADs 3 months: 61% 6 months: 58%	3 months: 49% (P=.024) 6 months: 46% (P=.025)	NR	NR
Capoccia 2004[26] IG=41 CG=33 3 outcome assessments over 12 months; extracted 12 month data Median(range)	All provider visits: median 9 range (0 to 42) Visits to PCP median 4 range (0 to 21)	median 9 range (0 to 60) (P=.99) median 5 range (0 to 17) (P=.88)	median 0 range (0 to 2)	median 0 range (0 to 2) (P=.27)	NR	NR	NR	NR	NR	NR
Finley 2003[28] IG=75 CG=50	PCP visits decreased 15%	increased 2% (P=.14)	Increased 7%	Increased 119% (P=.10)	NR	NR	Changed ADs 19% (14/75)	4% (2/50) (P=.016)	Drug cost 42% higher (P=.18)	
Finley 2002[29] IG=91 CG=129	To PCP decreased 39% (335 to 203)	decreased 12% (411 to 361) difference between changes (P=.007)	NR	NR	NR	NR	Changed ADs 24% (22/91)	5% (7/129) (P=.001)	NR	NR

AD = antidepressant medication; CG = control group; IG = intervention group; NR = not reported; PCP = primary care provider

Table 20. Goal Attainment Outcomes – Depression Studies

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal (n/N)	
		Pharmacy component	Control
No studies reporting			

CG = control group; IG = intervention group; NR = not reported

Table 21. Study and Intervention Characteristics – Diabetes Studies

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
McAdam-Marx 2015[53] Retro-spective cohort University-owned community-based primary care clinics	Patients with inadequately controlled T2DM (HbA1c<7%) Follow-up: max of18 months	Inclusion: -Intervention group: patients referred to diabetes collaborative care management (DCCM) by PCP; age ≥ 18; T2DM; treated at community clinic offering DCCM; treated ≥180 days prior to index date; follow-up care in clinic 3 to 18 months after index date -Control group: adults with T2DM treated at clinic without DCCM Exclusion: -HbA1c <7%	Improve patient outcomes Glycemic control (HbA1c) during 18 months post-index date	Clinical pharmacist	N=303 -Pharmacists able to prescribe and modify diabetes medication therapy, adjust insulin dosing, order HbA1c and lipid monitoring tests, and provide diabetes education - Follow-up visits included dose adjustments, adherence and disease education, and addressing patient questions *Mode/Frequency:* Initial in-person visit then telephone and in-person visits every 1-2 weeks until goals met or patient no longer engaged in program	N=394 Usual care	Referred to DCCM program by PCP; pharmacists worked under collaborative practice agreement with physicians and advanced practice clinicians
Skinner 2015[35] Retro-spective case-control Community health clinic	Uncontrolled diabetes 12-month study period	Inclusion: -age ≥ 18 -diabetes diagnosis -≥1 documented HbA1c>7% -a risk factor for disease-related microvascular complications -referred to MTM by PCP -clinical data from at least 3 clinic visits during a consecutive 12m period	Improve medication adherence and diabetes health outcomes	Clinical pharmacist	N=29 Medication Therapy Management -pharmacist reviewed patient's T2DM medication regimen -verbal education and training on medication delivery and best administration sites -education on health-promoting behaviors -patients asked to teach back the information to confirm understanding *Mode/Frequency:* mode not reported; frequency data not collected	N=29 (Matched sample – age, gender, race, ethnicity, BMI) -Usual care/no contact with clinical pharmacist	Referred to pharmacist for MTM by PCP

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Chung 2014[50] Retro-spective review via EMR CommUnity Care, outpatient clinics in Austin	Type1 or 2 diabetes mellitus 4-year study period 1 year follow-up for each patient	Inclusion: -age 18-89 -diagnosis of T1 or 2 DM -documentation of HbA1c ≥9% at baseline (3 months before or after index visit) -≥ 3 visits with clinical pharmacist or usual care provider -eligible for ≥ 1 yr before and after index dates -documented follow-up HbA1c Exclusion: -clinical pharmacy visit for any disease state before study initiation -diagnosis of cancer or HIV -pregnant -diagnosis code for motor vehicle accident or chronic pain	Assess the effect of clinical pharmacist involvement in a federally qualified health center on the change in A1c and frequency of diabetes related hospitalizations and ED visits 1 year post index change in A1c, diabetes-related hospitalizations, diabetes-related ED visits	Pharmacists who have completed at least 1 year of a postdoctoral residency training program	N=225 (matched N=220) -Implementing new medications -Titrating medications -Ordering laboratory panels -Counseling on lifestyle modification -Providing diabetes education -Managing associated comorbid conditions *Mode/Frequency:* -30 minute visit as often as needed or necessary to meet goals and/or for patient safety	N=557 (matched N=220) Usual care, followed by PCP and no appointments with a clinical pharmacist during study period	None mentioned

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Spence 2014[13] Retro-spective cohort Kaiser Permanent Southern California (KPSC) Region – outpatient pharmacy service	Non-adherent diabetes mellitus patients with HbA1c outside clinical goals 1 year after index date	Inclusion: -in KPSC's diabetes registry -non-adherent (Medication Possession Ratio <0.8) -on ≥1 oral medication for DM -at or above the HbA1c target of 8% -age >18 -enrolled with a pharmacy benefit for ≥1 year before and after index date Excluded: -active insulin prescription -resided in skilled nursing facility for >10 days or had received hospice care -OPCS patients that declined the consult	Improve medication adherence and likelihood of achieving clinical goals Not specified	Pharmacists participated in 5.5 hours of online and face to face training	N=359 Outpatient pharmacy clinical service (OPCS) program -B-SMART medication optimization process (identify barriers and assess readiness to change, provide solutions to adherence challenges, motivation, adherence tools, identify roles of health care team members, direct patients to other resources) -Pharmacist consult at time of prescription pick-up -Printing of a care management summary sheet -Spontaneous identification of non-adherent patients at the time the patient arrives at the pharmacy *Mode/Frequency:* -Face-to-face -One time (at prescription pick-up)	N=428 matched Did not receive an OPCS consultation	None noted
Brummel 2013[46] Non-randomized controlled trial Fairview Pharmacy Services, MN, Healthcare system	Diabetes 1 year of intervention and 1 year follow-up	Inclusion: -attended one of the clinics and decided to opt in to MTM program -all information on medications was available at baseline and all outcome measures were available for 2006, 2007, and 2008 -Control – those who didn't opt in to MTM program	Identify and resolve drug therapy problems and promote optimal patient outcomes Achieving optimal diabetes clinical management, determined with 5 component diabetes measure (D5)	MTM pharmacist	N=121 -Provided consultations using validated, standardized process -Pharmacists' responsibilities included assessing patient's medications, identification of patient's drug-related needs, resolution and prevention of drug-related problems, determining appropriate follow-up measures, and documentation of intervention outcomes -Initiate, modify, or discontinue drug therapy and order laboratory tests related to diabetes, hypertensions, and hyperlipidemia *Mode/Frequency:* -Primarily face-to-face	N=103 Usual care, not in MTM program	None mentioned

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Ip 2013[43] Dual-centered retro-spective study 2 Kaiser Permanente (KP) medical centers	Type 2 diabetes 12 months	Inclusion: -HbA1c >7% -type 2 diabetes -age > 18 -under the pharmacist's care for ≥ 2 months Exclusion: -type 1 diabetes -HbA1c<7% -patients who dis-enrolled from KP health insurance during the study time frame	Investigate the impact of pharmacist interventions on short-term clinical markers and long-term cardiovascular risk Change in HbA1c, LDL-C, & BP; rates of goal attainment; and change in predicted 10yr risk of coronary heart disease/stroke	Credentialed as certified diabetes educator and pharmacotherapy specialist	N=147 -Initial in-person visit with follow-up until therapeutic goals were met -Evaluated diabetes status and CV comorbidities -Pharmacotherapy modifications (prescribing and dosage adjustments) -Laboratory monitoring -Dietary and physical activity recommendations -Provision of diabetes self-care education -Physical assessments -Immunizations -Specialist referrals -Followed up for further care *Mode/Frequency:* -45-min face-to-face initial visit with follow-up in person or via telephone	N=147 PCP care (no pharmacist visit)	Referred by and discharged from program to PCP

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Heisler 2010/2012[3] [3,34] cRCT effectiveness study (team clusters randomized then patient randomized within team) 3 VA (2 academically affiliated) 2 KP facilities, primary care teams	Diabetes 14-month intervention period, patient discharged when adherence issues were addressed, BP was at target, statin was prescribed if indicated, and glycemic control addressed. Patients received a median of 9 weeks follow-up. Data also collected for the 6 months prior to and after the intervention period	Inclusion: In last 12 months -1 hospitalization or 2 outpatient visits with diabetes related code or ≥1 prescription for diabetes medication -most recent SBP≥140 and mean SBP (last 9 months) >140 or most recent SBP ≥150 and no other BP measures for last 9 months -poor refill adherence (gaps totaling ≥20% of days supply of ≥1 BP medication over prior year or insufficient medication intensification within 30 days prior to or any time after last BP (increase in number drug classes, daily dosage, or switch to another medication)) Exclusion: -pregnant -age < 18 or > 100 -impaired decision-making -KP patients excluded if on "no contact" list, hospitalized, nursing home resident, hospice or home health care; < 12 months of active drug benefit	BP control Relative change in systolic BP	Clinical pharmacist, trained in motivational interviewing and authorized to adjust BP and lipid medications	8 teams, N=2,319 with 1,797 activated -Proactive case identification using medication management tool database -Pharmacists referred to database which assisted in tracking and scheduling patient encounters and assessing adherence -Adherence counseling and assessment -Medication management -Recent clinical indicators discussed -Labs ordered -Medication changes could be made -Patients made/discussed goals -Pharmacist constructed specific, short-term action plan *Mode/Frequency:* -In-person or by telephone -Continued until patient was discharged from intervention program	8 teams, N=2,303 Usual care enhanced by information given to providers about patients' adherence and intensification problems; access to care manager and non-study clinical pharmacy services All patients; in-person or telephone intake by pharmacist plus welcome packet with educational materials	Copied provider on all clinical notes; alerted PCP when patient declined program, entered program or was discharged from program; pharmacists required to consult with PCP if patient was on 3 anti-hypertensives

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Jacobs 2012[38] RCT Ambulatory general internal medicine setting (Lahey clinic) in Burlington, MA	Type 2 diabetes 1 year	Inclusion: -age > 18 -documented HbA1c > 8% obtained more than 6 months earlier Exclusion: -receive primary care outside of Lahey Clinic Burlington campus -type 1 diabetes -HbA1c < 8% within 6 months -enrolled in another pharmacy or diabetes study -diabetes management by an outside endocrinologist -unable to adhere to study schedule	Improve glucose, lipid, and blood pressure control Achieving targets for HbA1c, LDL cholesterol, and blood pressure	5 clinical pharmacist practitioners who had PharmD degrees and minimum of post-graduate residency training with emphasis on ambulatory care practice with direct care for patients with chronic disease	N=72 Pharmacist visit included: -comprehensive medication review -targeted physical assessment -education on diabetes pathophysiology and importance of control -ordering laboratory tests -reviewing, modifying, and monitoring patients' medication therapy -detailed counseling on all therapies -facilitating self-monitoring of blood glucose -providing reinforcement of dietary guidelines and exercise -facilitate referrals to other clinicians *Mode/Frequency:* -Required to attend at least 3 clinic visits with pharmacist (baseline, 6 and 12 months)	N=92 Usual care as directed by physician according to current standard of practice	Therapy, monitoring, and referral recommenda-tions required approval by the patient's physician

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Salvo 2012[49] Retro-spective cohort County-funded health center, St. Louis	"Indigent" (low-income, minority) with diabetes (1 or 2) using insulin 2-year time frame	Inclusion -using insulin -ambulatory -speak English -age 18-64 -diabetes diagnosis Exclusion: -seeing an endocrinologist -from standard care if had current or previous interactions regarding diabetes management with pharmacy team	Glycemic control and preventive care measures Change in HbA1c between groups between baseline and various end points	Board-certified residency-trained pharmacist, full-time faculty member of the St. Louis College of Pharmacy and pharmacy resident and students	N=69 Pharmacist-managed insulin titration program -Initially meeting: discuss diabetes management, role of preventive care measures, self-monitored blood glucose, complications, and pharmacist program -Review medical record to determine need for medication initiation, adjustment or discontinuation, lab monitoring, and preventive care measures -Follow-up (telephone) every 1-2 weeks: patient reports insulin regimen, self-monitored blood glucose, adverse events. -Assess adherence, educate on lifestyle modifications and medication adherence, adjust insulin dosage -Preventive care assessment at each interaction -Schedule appointments with specialists (podiatrist, dietician) *Mode/Frequency:* -Initial in-person meeting then telephone follow-up every 1-2 weeks	N=57 matched Standard care	Pharmacist notifies PCP of insulin adjustments and reminds of overdue lab work/vaccines

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Cohen 2011[32] RCT (VA-MEDIC-E) Primary care, VA, urban (Providence)	Type 2 diabetes 6 months	Inclusion: -type 2 diabetes - HbA1c>7%; LDL>100mg/dL or >70mg/dL if CAD; BP>130/80 mmHg (each documented in last 6 months) -willing to discuss diabetes and cardiac risk factors in group setting Exclusion: -gestational diabetes -unable to attend sessions -condition precluding diabetes self-care	CV Risk Reduction Primary Outcome: change in proportion of participants achieving target glycemic and cardiac risk factor goals	Clinical pharmacist, trained in diabetes education with prescribing privileges	N=50 Regular visits with PCP plus -Education -Behavioral and pharmacologic interventions for hypertension, hyperlipidemia, hyperglycemia, and tobacco use -Received CV report card and exercise prescription, set diet and activity goals -Medication regimens discussed and evaluated, doses titrated -Referrals *Mode/Frequency:* -4 once-weekly 2-hour educational sessions (1 hour education, 1 hour behavioral and pharmacologic interventions) -5 monthly booster sessions	N=49 Standard Primary care, average. once every 4 months, 20-60 minute appointments, may include referrals	Education session provided by pharmacist, dietitian, nurse and physical therapist -also saw PCP
Padiyara 2011[45] Retro-spective EMR review Primary care clinic affiliated with multi-specialty medical group; suburban metropolitan area	Diagnosed with diabetes mellitus 1 year	Inclusion -age ≥18 -2 or more visits with the pharmacist-managed diabetes clinic during study period (control group had at least 2 PCP visits and no pharmacist clinic visits)	Educate and directly manage drug therapy and preventive care services	3 university-affiliated pharmacists	N=321 -Emphasized the ADA guidelines -Pharmacists have autonomy in: -assessing patients -providing disease-state education -reviewing current medication lists -initiating or adjusting medication therapy -ordering laboratory tests -determining appropriate follow-up *Mode/Frequency* -45-minute initial meeting; 30-minute visits for returning patients; had at least 2 pharmacist or PCP visits to be included in study	N=321 randomly selected Usual care includes provision of preventive care services and screenings; medication management; education of patient by PCP, or other staff; and referral to other specialist if appropriate	Some patients referred to pharmacist clinic by PCP

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Pape 2011[48] Prospective cRCT (clinics randomized) Providence Primary Care Research Network, internal medicine/ family practice clinics (Oregon)	Diabetes	Inclusion: -problem list entry of diabetes on EMR -age ≥ 18 Exclusion: -no evidence of medical chart activity within 3 years	Cholesterol management in diabetes Proportion of participants in each arm achieving a target LDL-C level < 100mg/dL	Clinical pharmacists	6 clinics, N=4,160 Health IT resources plus -Reviewed medical charts of patients with elevated LDL-C level -Developed individualized, evidence-based treatment recommendations to include medication therapy and follow-up laboratory monitoring -Treatment plan sent to PCP for review -Physician could ignore recommendation, act on it or approve intervention by pharmacist *Mode/Frequency:* -If intervention approved: pharmacist contacted patient by phone, education provided to support a shared decision-making process for treatment plan	3 clinics, N=2,069 Clinics randomized to control had access to CareManager disease management software which provided automated quality reporting, benchmarking, and robust care opportunity decision support	Treatment plan shared with PCP who could decide how to react Pharmacist supported by medical assistant who triaged lab results, ordered overdue labs, scheduled appointments, and facilitated mailings (by protocol)

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Taveira[30] 2011 RCT (VA-MEDIC-D) Providence VA Medical Center	Type 1 or Type 2 diabetes AND depression 6 months	Inclusion: -type 1 or 2 diabetes -age ≥ 18 -HbA1c >6.5% within last 6 months -concomitant depression -willing to discuss diabetes and cardiovascular risk factors in group setting Exclusion: -gestational DM -unable to attend group session -disease condition, psychiatric instability, or organic brain injury precluding diabetes self-care	Management of diabetes and CV risk factors Change in proportion of participants who attained a goal HbA1c of <7% at 6 months	Clinical pharmacist with prescribing authority and certified diabetes educator	N=44 -Regular visits with PDP and standard visits with mental health provider -Education part of session: interactive lectures presented by a nurse, nutritionist, or clinical pharmacists, focused on self-care behaviors (*eg*, goal setting, promoting healthy problem solving) -Food logs reviewed by pharmacist and participants reminded of nutritional goals -Pharmacological and Behavioral intervention: conducted by clinical pharmacist, group assessment to determine degree to which patients felt they could manage their diabetes care daily, group counseling, reinforcement to enhance self-efficacy -Participants provided with CV risk report cards with medical history, medications, vitals, and laboratory values, reviewed during week 1 session, updated regularly -Medications titrated and initiated (no changes to psychiatric medications) -Individualized homework for medication changes and behavior change goals *Mode/Frequency:* -4 once-weekly sessions of 2 hours, then 5 monthly booster sessions held in classroom with 4-6 participants	N=44 -regular visits with primary care provider, approximately 30 minutes -referral to Diabetes Self-management Education Program (4 weekly education visits and monthly 90 minute follow-up appointments) -continue standard care with mental health providers	Education part of session presented by nurse or nutritionist too

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Jameson 2010[36] RCT Community based primary care group (Advantage Health Physician Network) 13 offices, 3 urban, 9 suburban 1 rural	Diabetes 12 months	Inclusion: -age ≥18 -HbA1c ≥9% or no office visit within 12 months Exclusion: -being seen by an endocrinologist -not expected to live for duration of study	Improved management Change in HbA1c after 1 year	Board-certified pharmaco-therapy specialist with diabetes management and education training	N=52 Targeted patient outreach plus -assessment of adherence, barriers to optimizing blood glucose levels, and medication regimen -individualized education on self-management (diet, exercise, blood glucose level testing, medications, insulin) -followed guidelines of the Management of Type 2 Diabetes, including changing medication *Mode/Frequency:* -Initial home visit with study nurse to determine eligibility -In-person session with pharmacist at primary care site -Follow-up visits supplemented with phone calls	N=51 Usual care including registries to identify and track patients and targeted patient outreach	PCP approved any changes in medication or therapy
Johnson 2010[42] Retro-spective chart review "safety net" clinic medical homes, major urban city	Uninsured or underinsured with type 2 diabetes 2 years (mean 1.2 years for intervention group; 1.4 years for control group)	Inclusion: -HbA1c >9% -had a clinic visit during enrollment period -Age > 18 -second visit with HbA1c within 2 years of index visit -for intervention group: referred to pharmacist by usual provider	Disease management Change in A1c from baseline to last measured post-treatment A1c and whether or not the patient achieved the treatment goal of a final A1c<7%	Clinical pharmacist	N=222 -Reviewing medical, laboratory, and medication histories -Evaluating and modifying drug therapy under an established protocol -Ordering routine laboratory tests (HbA1c, lipid panel, metabolic panel, renal and liver function) -Monitoring adherence to drug therapy regimens -Educating patients -Providing follow-up care *Mode/Frequency:* -At least 2 clinic visits with laboratory value measurements	N=262 not matched Usual care no pharmacist	Referred by PCP

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Taveira 2010[31] RCT (VA-MEDIC) Providence VA Medical Center	Type 2 diabetes 1 month-long intervention, follow-up at 4 months (3 months post)	Inclusion: -type 2 diabetes -age ≥18 -HbA1c 7% to 9% within previous 6 months -Willing to discuss diabetes and cardiovascular risk factors in group settings Exclusion: -unable to attend group settings -disease condition precluding diabetes self-care	Reduce cardiac risk factors Improve achievement of target goals in hypertension, hyperglycemia, hyperlipidemia, and tobacco use	Clinical pharmacists with prescriptive authority; certified in diabetes education and physical assessment with 6 months supervised pharmacy management	N=58 Regular PCP appointments plus -educational part of session: interactive lectures provided by nurse, nutritionist, physical therapist, or clinical pharmacist focused on diabetes self-care behaviors -behavior and pharmacological portion of session with clinical pharmacist: discussed and titrated medication regimens based on algorithms, wrote down medication changes, help with tobacco cessation, patients taught to carry CV risk report cards (see above) *Mode/Frequency:* -4 weekly, 2-hr sessions in a classroom setting with approximately 4-8 participants	N=51 Saw primary care provider at VA medical center through individual clinic visits, average frequency 4 months	Educational sessions also provided by nurse, nutritionist, and physical therapist
Fox 2009[47] Non-equivalent group, quasi-experimental study Florida Healthcare Plans HMO	Diabetes and Medicare part D, MTM eligible (≥ 3 chronic diseases and ≥ 4 maintenance medication and likely Part D medication costs ≥ $4000/year 1 year	Inclusion: -Medicare Part D member -eligible for comprehensive diabetes care (CDC) according to HEDIS -MTM eligible (3 or more chronic diseases and 4 or more maintenance medications and likely to have Medicare part D costs of >$4,000/yr) and chose to participate	Improve HEDIS LDL-C quality measures for CDC Presence of LDL-C screening, LDL-C values, and LCL-C control	Staff clinical pharmacists	N=255 -Medication therapy review and evaluation, sent to PCP; included: -drug-drug and drug-disease interactions -OTC drug therapy -medication monitoring, recommending changes if indicated -adherence to HEDIS comprehensive diabetes care guidelines and goals (LDL-C control and HbA1c, BP, and weight) -medication cost reduction -adherence counseling -adverse events, education -medication optimization, reducing cost and consolidating (not limited to lipid-lowering medications) *Mode/Frequency:* -Telephone interview with pharmacist and follow-up calls if recommendations made (at least 3 calls)	Usual care – 2 groups 1) N=56 who did not participate in MTM 2) N=1,803 enrollees not eligible for MTM	Recommendations shared with physician

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Scott 2006[40] RCT Siouxland Community Health Center in Sioux City, Iowa	Type 2 diabetes Intervention for 3 months, total of 9 month follow-up	Inclusion: -SCHC members -age >18 -diagnosis of type 2 diabetes -referred by PCP Exclusion: -patient foresaw difficulty completing the study -migrant worker -drug abuse	Manage patients' diabetes Reduction of HbA1c levels	Clinical pharmacist with 1 year primary care residency program	N=76 -Appointments focused on disease management, lifestyle adjustments, and goal setting -Group sessions: reviewed nutrition and basic diabetes management (nurse and dietitian participated) -pharmacist provided other therapeutic interventions (*eg,* aspirin therapy, influenza vaccine) and reminded patients about appointments *Mode/Frequency:* -Appointments every 2 weeks -Group-session appointments and telephone follow-up when necessary	N=73 Standard diabetes care, managed by a nurse All patients had appointments at baseline and 3, 6, & 9 months; incentive package for attending study appointments	Group appointments involved a pharmacist, dietitian, and nurse; medication change recommendations were given to provider and implemented by provider or pharmacist
Odegard 2005[51] RCT University of WA neighbor-hood primary care clinics, greater Seattle area	Type 2 diabetes 6 month intervention plus 6 month follow-up after intervention ended	Inclusion: -age ≥ 18 -type 2 diabetes -taking at least one oral diabetes medication -HbA1c ≥9% Exclusion: -non-English speaking -unstable psychiatric condition -terminal prognosis (within 6 months)	Improving diabetes control HbA1c levels	Primary care pharmacist	N=43 -Development of a diabetes care plan -Regular pharmacist-patient communication on diabetes care progress -Pharmacist-provider communication on diabetes care progress -Medication-related problems requiring intervention identified *Mode/Frequency:* -Initial in-person appointment then weekly in-person or telephone contact (decreased to monthly once care needs were progressing)	N=34 Baseline interview and continue normal care with PCP	Diabetes care plan was communicated to PCP through EMR notation, communication between pharmacist and PCP

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Rothman 2005[39] cRCT (clinics matched and randomized) University of NC General Internal Medicine Practice	Vulnerable patients with poorly controlled type 2 diabetes February 2001 to April 2003, patients followed for 1 year	Inclusion: -age ≥ 18 -diagnosed with type 2 diabetes -followed for diabetes care in the practice -referred by provider -poor glucose control (HbA1c≥8%) -spoke English -life expectancy >6 months	Improve cardiovascular risk factors and HbA1c levels Blood pressure, A1c levels, cholesterol level, and aspirin use	Clinical pharmacist who could initiate and increase use of blood pressure-, cholesterol-, and glucose-lowering medications	N=105 Usual care plus -Management session: diabetes education, treatment recommendations to PCP -Intensive education sessions, counseling -Medication management -Evidence-based algorithms to initiate and increase use of blood pressure, cholesterol, and glucose lowering medications -Proactive management of clinical parameters -Diabetes care coordinator to address issues related to health behavior and education, remind of appointments, and help address barriers to care *Mode/Frequency:* -1 hour management session -Dedicated clinical slots for intervention group patients -Pharmacist contacted patients at least every 2-4 weeks	N=112 Management session plus usual care from PCP	Results from sessions with pharmacists shared with PCP Medication adjustments approved (before or after as requested by PCP)

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Shane-McWhorter 2005[41] Retro-spective review Community health center, Utah; clinical pharmacy demonstra-tion project	Diabetes Charts were reviewed for all patients who received diabetes education from August 2000-June 2002 Outcomes collected over 1-3 years	Inclusion: -received at least one education session (IG) -diabetes	Enhancing patient care in the area of drug therapy and disease management No primary outcome specified	College of Pharmacy faculty clinician, certified diabetes educator	N=176 -Initial chart review: assess drug therapy, need for test/monitoring, health care maintenance needs, establish plan of action/education plan, evaluate appropriateness of drug therapies to look for potential interactions/adverse reactions -In-person patient education regarding diabetes, hypertension, hyperlipidemia, drug therapy, lifestyle modifications, ADA as components of self-management education -Individualized recommendations regarding drug therapy, lab testing, and healthcare maintenance -Obtained a detailed medical and drug therapy history -Needs assessment -Recommendations for provider regarding maintaining, changing, or adding drugs, certain tests, health care maintenance (made in chart note) -Follow-up education to document changes made by patient in nutrition or exercise, provide drug therapy education, information about health care maintenance and complications, determine if any tests still required -Chart reviews on continuing basis to track outcomes and provide recommendations *Mode/Frequency:* -In person -Monitoring 3 times/year (chart review)	N=176 randomly selected Access to a non-pharmacist health educator	Made recommenda-tions to physician

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Stroup 2003[52] RCT The Endocrine Group, Albany NY, associated with the Albany College of Pharmacy	Poorly controlled diabetes mellitus 2 years	Inclusion: -patient at The Endocrine Group -minimum 1 year duration of HbA1c values greater than 10% -physician approved	Improve glycemic control Average HbA1c values over a 2yr period	2 consecutive groups of 6 fourth-year pharmacy students who had completed a 1-semester didactic program and shadowed a faculty member or more experienced student	N=30 -Students reviewed with each patient: -compliance with therapies -side effects, recent ED visits or hospitalizations -blood glucose monitoring -blood sugar logs -hypoglycemic management including insulin therapy and dosage adjustment -goals of therapy -diabetes complications -patient-initiated questions -diet, exercise, and weight loss -Notes from visit were typed and delivered to endocrinologist and submitted into EMR *Mode/Frequency:* -Monthly hour-long visits in patients' home	N=40 See physician as typically scheduled (every 3-4 months)	Acute problems immediately communicated verbally to patients' endocrinologists; notes from visit delivered to endocrinologist
Kelly 2000[44] CCT Richmond Health Care Group, a managed care-affiliated physicians group in Virginia	Diabetes 9 months	Inclusion: -diabetic patients taking oral diabetic agents or insulin -chosen by their providers to participate -documented HbA1c >8%, systolic >130mm Hg or diastolic >85mmHg, or LDL-c >120% of goal	Achieving near normoglycemia, lowering blood pressure, and LDL <130 mg/dL in patients with 2 or more CV risk factors or <100 mg/dL for patients with established disease HbA1c, SBP,DBP, and smoking cessation	Clinical site included one full-time clinical pharmacist/ faculty member, one pharmacy resident, and fourth-year Doctor of Pharmacy students	N=32 -Assessment/consultation on diabetes self-management -Complete medical history -Laboratory tests -Develop management plan, create short- and long-term goals, assess medication issues, and review nutrition recommendations, lifestyle changes, and blood-glucose monitoring instructions -Follow-up: reviewed goals, self-management plan, medications, hypoglycemic events, test results and lifestyle changes -Continuing education on self-management topics *Mode/Frequency:* -One-on-one assessment/consultation -Follow-up scheduled based on degree of monitoring required (usually monthly)	N=16 matched Historical controls, one year prior to implementation of clinical service	Dosage adjustments made in collaboration with PCP

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Jaber 1996[37] RCT University-affiliated internal medicine outpatient clinic, urban, Detroit	Urban African-Americans with non-insulin-dependent diabetes mellitus (NIDDM) 4 months	Inclusion: -urban African-American patients -NIDDM -attending outpatient clinic Exclusion: -insulin-dependent DM -renal dysfunction -hepatic disorder -significant cardiac complications within 6 months -mental incompetence -history of non-compliance with regular clinic visits in past 2 years	Manage NIDDM diabetes in African-Americans Fasting plasma glucose and glycated hemoglobin concentrations	Pharmacist with full-prescribing authority for hypoglycemic agents	N=28 randomized -Diabetes-specific pharmacotherapeutic evaluation and dosage adjustment -Comprehensive and individualized patient education on diabetes and its complications -Training on the recognition and treatment of hypoglycemia and hyperglycemia -Medication counseling -Specific instructions on dietary regulation and an exercise plan -Training for self-monitoring of blood glucose -Adjusted or titrated hypoglycemic therapeutic regimens *Mode/Frequency:* -Follow-up on scheduled weekly basis until targeted glycemic control reached, then clinic visit every 2-4 weeks	N=17 randomized -reported to clinic for initial assessment and final exit visit -instructed to continue to receive standard care from PCP (every 3-4 months)	None reported

T2DM = type 2 diabetes; CAD = coronary artery disease; cRCT = cluster randomized controlled trial; CV = cardiovascular; LDL = low-density lipoprotein; VA = Veterans Affairs; KP = Kaiser Permanente; BP = blood pressure; DM = diabetes mellitus; SBP = systolic blood pressure; EMR = electronic medical record; SCHC = Siouxland Community Health Center; NIDDM = non-insulin-dependent diabetes mellitus; OTC = over the counter; PCP = primary care provider; HEDIS = healthcare effectiveness data and information set; HbA1c = glycosylated hemoglobin; ADA = American diabetes association; ED = emergency department; MTM = medication therapy management; DBP = diastolic blood pressure; RCT = randomized controlled trial

Table 22. Drug-related Problems Outcomes – Diabetes Studies

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Skinner 2015 IG=29[35] CG=29	NR	NR	NR	NR	NR	NR	Medication adherent (refilled at least 85% of the time) 62%	7% (P<.001)	NR	NR
Spence 2014[13] IG=359 CG=428	NR	NR	NR	NR	NR	NR	53.5% (192/359) adherent Mean MPR 0.78 (0.2) Discontinued 11.7% (42/359)	37.4% (160/428) adherent (P=.001) Mean MPR 0.74 (0.2) (P=.091) Discontinued 35.5% (152/428) (P=.001)	NR	NR
Jacobs 2012[38] IG=72 CG=92	NR	NR	NR	NR	NR	NR	NR	NR	No adverse events caused by study protocol	
Cohen 2011[32] IG=50 CG=49	NR	NR	NR	NR	NR	NR	Total[a] medication possession ratio: 0.87	0.83 (P=.19)	NR	NR
Jameson 2010[36] IG=52 CG=51	NR	NR	NR	NR	NR	NR	NR	NR	1 severe hypoglycemic event in intervention group (events could not be assessed in control group)	

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Odegard 2005[51] IG=43 CG=34	Diabetes Medications Mean (SD) MAI scores at baseline: 1.1 (1.5) 6 months: 0.6 (0.7) 1 year: 0.8 (1.0)	Mean MAI scores at baseline: 0.8 (1.0) 6 months: 0.8 (1.4) 1 year: 0.6 (0.7) Appropriate-ness of diabetes medications : P=.65 between groups over study period	NR	NR	NR	NR	Intervention had no effect on improving adherence during study period		NR	NR
Rothman 2005[39] IG=112, 6months 105, 1yr 99 CG=105, 6months 99, 1yr 95	NR	NR	NR	NR	NR	NR	NR	NR	Rate of events from 6-12 months follow-up Hypoglycemic episodes 1.3 Hypotensive episodes 0.1	Hypoglycemic episodes 1.0 (Rate ratio 1.3 [0.6, 2.5]) Hypotensive episodes 0.2 (Rate ratio 0.3 ([0.1, 1.6])
Jaber 1996[37] IG=17 CG=22	NR	NR	NR	NR	NR	NR	NR	NR	17 hypoglycemic reactions (mild to moderate; self-treated)	2 hypoglycemic reactions (mild to moderate; self-treated)

CG=control group; IG=intervention group; MAI=medication appropriateness index; NR = not reported
[a] Antihypertensive, cholesterol, and diabetes medications

Table 23. Mortality, Quality of Life, Access, and Patient Satisfaction Outcomes – Diabetes Studies

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Cohen 2011[32] IG=50 CG=49	4% (2/50)	2% (1/49) P = NS[b]	VR-36 Mean change: Physical 1.65 Mental 0.48 (both P=NS from baseline)	Physical -1.95 Mental 0.78 (both P=NS from baseline)	NR	NR	NR	NR
Pape 2011[48] IG=3 clinics, 23 physicians, 2069 patients CG=6 clinics, 45 physicians, 4160 patients	NR	NR	NR	NR	Satisfaction with reaching someone in an emergency[a] 84%	77% (P=.04)	Overall satisfaction[a] 5.4 (0.9)	5.2 (1.1) (P=.15)
Taveira 2011[30] IG=44 CG=44	All-cause NR No diabetes-related death in either group		NR	NR	NR	NR	NR	NR
Scott 2006[40] IG=64 CG=67	NR	NR	Total DQOL score - change from baseline to month 9 24.4	14.8 (P=NR)	NR	NR	DQOL score - satisfaction measure - change from baseline to month 9 13.7	6.4 (P=.007)
Rothman 2005[39] IG=112, 6months 105, 1yr 99 CG=105, 6months 99, 1yr 95	1.8% (2/112)	3.8% (4/105) (P=.43)[b]	NR	NR	NR	NR	DTSQ +8 over 12 months of intervention	+4 over 12 months of intervention Difference: +3 (1, 6) (P<.05)
Jaber 1996[37] IG=17 CG=22	NR	NR	Groups similar for any domain of Health Status Questionnaire (version 2.0)		NR	NR	NR	NR

ADA = American Diabetes Association; CG = control group; DQOL=Diabetes Quality of life Questionnaire; DTSQ = Diabetes Treatment Satisfaction Questionnaire; IG = intervention group; NR = not reported; NS = not statistically significant; VR-36 = SF-36 for Veterans

[a] Assessed using ADA and National Committee for Quality Assurance Provider Recognition Program Modified Patient Satisfaction Survey

[b] Calculated P value (not reported in study)

Table 24. Healthcare Utilization and Cost Outcomes – Diabetes Studies

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
McAdam-Marx 2015[53] IG=303 CG=394	Outpatient utilization: Mean (SD) difference pre to post intervention 1.16 (6.81)	0.61 (3.93) (P<.001) between groups	Mean (SD) difference pre to post intervention 0.07 (1.28)	0.04 (0.35) (P=.78) between groups	Inpatient utilization Mean (SD) difference pre to post intervention -0.01 (0.69)	0.01 (0.30) (P=0.56) between groups	NR	NR	Total patient charges Mean (SD) difference pre to post intervention $251 ($18,173)	$1,341 ($14,475) (P=0.04) between groups
Chung 2014[50] IG=220 CG=220	NR	NR	Increase of 4 visits per 220 patients from pre-index to post-index year (mean 0.018)	Increase of 16 visits per 220 patients (mean 0.073) (P=.18)	Decrease of 1 hospital-ization for 220 patients from pre-index to post-index year (mean -0.005)	Increase of 8 hospital-izations for 220 patients (mean 0.036) (P=.06)	NR	NR	NR	NR
Spence 2014[13] IG=359 CG=428	NR	NR	1.7% (6/359)	14.2% (18/428) (P=.04)	0.6% (2/359)	1.4% (6/428) (P=.24)	NR	NR	$5.79 saved for every dollar spent on program (including coronary artery disease program)	
Brummel 2013[46] IG=121 CG=103	NR	NR	NR	NR	NR	NR	Daily Aspirin use Baseline 97.5% Post intervention 100% Follow-up 99.2%	Baseline 93.3% Post Intervention 98.1% Follow-up 99.0% (all P=NS between groups)	NR	NR

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Ip 2013[43] IG=147 CG=147	NR	NR	NR	NR	NR	NR	NR	NR	10 year CHD risk: decreased from 16.4 to 9.3% 10 year stroke risk: decreased from 7.6 to 6.8%	10 year CHD risk: decreased from 17.4 to 14.8% (P<.001 vs intervention) 10 year stroke risk: no change (P=.001 vs intervention)
Heisler 2010/2012[33,34] IG=1797 patients, 8 primary care teams CG=2303 patients, 8 primary care teams	Primary care visits mean (SD) 4.6 (5.9)	4.3 (6.1) (P=.10)	24% (434/1797)	23% (532/2303) (P=.43)	13% (227/1797)	13% (300/2303) (P=.71)	Proportion of patients with BP medication changes 69.7% (1253/1797)	Proportion of patients with BP medication changes 63% (1451/2303) (P<.01)	NR	NR
Jacobs 2012[38] IG=72 CG=92	NR	NR	NR	NR	NR	NR	Increase in number of meds during study period: 1.2 Number of meds at end of study: 7.1	Increase in number of meds during study period: 0.9 (P=NS) Number at end of study: 6.0 (P=.03)	NR	NR

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Salvo 2012[49] IG=69 CG=57	NR	NR	NR	NR	NR	NR	Increase in total daily insulin dose: 33 units (mean) (P=.004 compared to control at end of study) Bolus insulin added for 11 patients	Bolus insulin added for 1 patient (P=NR)	Influenza vaccine 70% (48/69) Pneumo-coccal vaccine 67% (46/69) Dietitian visit 39% (27/69)	Influenza 52% (30/57) (P=.03) Pneumococcal 40% (23/57) (P=.003) Dietitian 16% (9/57) (P=.003)
Cohen 2011[32] IG=50 CG=49	PCP visits in 6 months (mean) 1.56	1.65 (P=NR)	NR	NR	NR	NR	At 6 months: Total antihyper-tensive meds 2.34 (1.22) Diabetes meds 1.64 (0.78) Cholesterol meds 1.00 (0.49)	At end: Total antihyper-tensive meds 1.94 (1.18) (P<.001) Diabetes meds 1.41 (0.73) (P=.03) Cholesterol meds 0.86 (0.41) (P=.006)	NR	NR
Padiyara 2011[45] IG=321 CG=321	NR	NR	NR	NR	NR	NR	Take an aspirin at least 15x/month 280/321)	42.4% (136/321) (P<.001)	NR	NR
Pape 2011[48] IG=3 clinics, 23 physicians, 2069 patients CG=6 clinics, 45 physicians, 4160 patients	NR	NR	NR	NR	NR	NR	Any lipid lowering medication 77% Statin prescription 75%	Any lipid lowering medication 63% (P=.04) Statin prescription 60% (P=.01)	NR	NR

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Taveira 2011[30] IG=44 CG=44	0.3 (0.6)	0.3 (0.6) (P=.70)	All cause 39.5% Diabetes-related 2.3%	All cause 39.5% (P=NS) Diabetes-related 4.7% (P=.60)	14%	16.3% (P=.80) No admissions were diabetes-related	Dose increase or initiation: antihyper-tensive 68.2% antihyper-glycemic agent 81.8% antihyper-lipidemic 52.3% antidepres-sants 29.6%	Dose increase or initiation: antihyper-tensive 34.9% (P=.003) antihyper-glycemic agent 58.1% (P=.02) antihyper-lipidemic 39.5% (P=.28) antidepres-sants 25.0% (P=.81)	Over 6 months: Mean of 6.6 medical appointments Mean of 1.2 (0.8) PCP visits	Mean of 1.3 (0.9) PCP visits Mean of 0.6 (1.2) Diabetes Self-Managemen t Education visits (P=NR)
Jameson 2010[36] IG=52 CG=51	NR	NR	NR	NR	NR	NR	Basal-bolus insulin started 28.8% (15/52) Discontinued oral medication 28.8% (15/52)	Basal-bolus insulin started 2% (1/51) (P=.0002)[a] Discontinued oral medication 2% (1/51) (P=.0002)[a]	NR	NR
Taveira 2010[31] IG=58 CG=51	NR	NR	NR	NR	NR	NR	Aspirin added 5.3% Statin added 7% Insulin added 15.8% Niacin added 17.5%	Aspirin added 4.0% (P=NS between groups) Statin added 5.9% (P<.05) Insulin added 2% (P<.05) Niacin added 2% (P<.05)	NR	NR

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Fox 2009[47] IG (MTM participants)=255 CG1 (MTM non-participants)=56 CG2 (Not MTM eligible, CDC)=1,803	NR	NR	NR	NR	NR	NR	Change in number of prescriptions per month during year post intervention -4.08%	-2.84% (P=NR)	Change in year following intervention Total drug costs -18.4% Total Part D copay -4.0% Total copay -5.5%	Total drug costs -7.0% Total Part D copay 4.2% Total copay -1.5% (P=NR)
Scott 2006[40] IG=64 CG=67	NR	NR	Urgent Care: RR 0.8 (0.4, 1.6) ER: RR 0.8 (0.5, 1.4)		NR	NR	Aspirin therapy achieved: 81% (52/64)	46% (31/67) (P=.02)	NR	NR
Odegard 2005[51] IG=43 CG=34	Mean (SD) 3.2 (1.5) over 12 months	5.4 (2.4) over 12 months (P=NR)	NR	NR	NR	NR	NR	NR	NR	NR
Rothman 2005[39] IG=112, 6months 105, 1yr 99 CG=105, 6months 99, 1yr 95	Rate of event from 6-12 month follow-up 2.0	1.9 (Rate ratio 1.1 [0.9, 1.3])	Rate of event from 6-12 month follow-up, Urgent care 0.2 ED visits 0.4	Urgent care 0.2 (Rate Ratio 0.8 [0.4, 1.6]) ED visits 0.5 (Rate Ratio 0.8 [0.5, 1.4])	Rate of event from 6-12 month follow-up 0.2	0.2 (Rate Ratio 1.1 [0.6, 2.0])	Use of aspirin at 12 months 91% (87/96)	Use of aspirin 58% (54/93) (P<.0001)	NR	NR
Shane-McWhorter 2005[41] IG=176 CG=176	NR	NR	NR	NR	NR	NR	Aspirin prescribed 55.1% (97/176)	64.7% (114/176) (P=.08)[a]	Immuniza-tions 1.25/pt DM education documented 100% (176/176)	0.95/pt (P<.006) 19.3% (34/176) (P<.001)

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Stroup 2003[52] IG=30 CG=40	NR	NR	6.7% (2/30) had 2 visits over 2 years - both diabetes related	27.5% (11/40) had 16 visits (P=.03) 8 patients had diabetes-related visits (P=.115)	14 admissions in 13/30 patients (43%) 8 patients had diabetes-related admissions	32 admissions in 20/40 patients (50%) 14 patients had diabetes-related admissions (P=.58 for admissions; P=.29 for DM related)	NR	NR	NR	NR
Jaber 1996[37] IG=17 CG=22	NR	NR	NR	NR	5.6% (1/17) hospitalization (chest pain)	9.1% (2/22) hospitalizations (non-DM related) (P=NS)[a]	38 pharma-cotherapeutic interventions (mean 2.2/pt)	9 pharma-cotherapeutic interventions (mean 0.4/pt) (P=NR)	NR	NR

BP = blood pressure; CG = control group; CHD = coronary heart disease; DM = diabetes mellitus; ED=emergency department; IG = intervention group; NR = not reported; PCP = primary care provider; SD = standard deviation

[a] Calculated P value (not reported in study)

Table 25. Goal Attainment Outcomes – Diabetes Studies

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal (n/N)	
		Pharmacy component	Control
Brummel 2013[46] IG=121 CG=103	HbA1c<7% LDL <100mg/dL BP <130/80 mmHg Tobacco Free Optimal Score	*HbA1c* Baseline 43.8%[b] Post intervention 73.55%[a] Follow-up 42.15%[ab] *LDL* Baseline 63.64% Post intervention 83.47%[a] Follow-up 79.34% *Blood Pressure* Baseline 66.12% Post intervention 71.07% Follow-up 76.03% *Tobacco Free* Baseline 85.95% Post intervention 91.74%[ab] Follow-up 91.74%[b] *Optimal Score* Baseline 21.49% Post Intervention 45.45% (P<.001) Follow-up 25.62% (P=.0002)	*HbA1c* Baseline 63.11% Post Intervention 72.82% Follow-up 59.22% *LDL* Baseline 65.05% Post Intervention 73.79% Follow-up 73.79% *Blood Pressure* Baseline 61.17% Post Intervention 72.82% Follow-up 69.9% *Tobacco Free* Baseline 79.61% Post Intervention 81.55% Follow-up 82.52% *Optimal Score* Baseline 24.27% Post intervention 39.81% (P=.0002) Follow-up 30.10% (P=.08)
Ip 2013[43] IG=147 CG=147	HbA1c <7% LDL <100mg/dL BP <130/80 mm Hg All three goals	At 12 months HbA1c 62.6% (OR 3.9, P<.0001) LDL 85% (OR 2.0, P=.02) BP 61.9% (OR 2.0, P=.002) All 3 36.7% (OR 3.2, P=.0004) P<.001 for each of the three, NSR for “all 3”	At 12 months HbA1c 28.6% LDL 57.5% BP 43.5% All 3 9.5%
Jacobs 2012[38] IG=72 CG=92	HbA1c<7% LDL-C <100mg/dL BP<130/80 mm Hg	HbA1c 12 months 35% (19/55) LDL-C 12 months 62% (32/52) SBP 12 months 51% (29/57) DBP 12 months 84% (48/57)	HbA1c 12 months 21% (14/67) (P=.11) LDL-C 12 months 55% (24/44) (P=.54) SBP 12 months 43% (30/70) (P=.38) DBP 12 months 77% (54/70) (P=.37)
Salvo 2012[49] IG=69 CG=57	HbA1c <7%	20.3%	14% p=.48
Cohen 2011[32] IG=50 CG=49	Recommended by the ADA: SBP<130mm Hg LDL<100mg/dL HbA1c<7%	HbA1c 40.8% (OR 2.73 [1.03, 7.26]) SBP 58% (OR 3.06 [1.31, 7.16]) LDL 82% Combined 16.0%	HbA1c 20.4% (P=.03) SBP 32.7% (P=.02) LDL 65.3% (P=.06) Combined 4.1% (P=.049)

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal (n/N)	
		Pharmacy component	Control
Padiyara 2011[45] IG=321 CG=321	BP<130/80 mm Hg LDL-C <100mg/dL HbA1c <7% Documented A1c in last 6 months Received formal diabetes education	44.6% (120/269) 76% (244/321) 50.8% (163/321) 100% (321/321) 93.4% (300/321)	48% (123/256) P=.43 59.2% (190/321) P<.001 71% (228/321) P<.001 99.7% (320/321) P=.317 40.2% (129/321) P<.001
Pape 2011[48] IG=3 clinics, 23 physicians, 2069 patients CG=6 clinics, 45 physicians, 4160 patients	LDL-C <100mg/dL HbA1c <7% BP <130/80mm Hg	LDL-C 78% (OR 2.8 [2.2, 3.7]) HbA1c 51% BP 55%	LDL-C 50% (P=.003) HbA1c 49% (P=.81) BP 49% (P=.22)
Taveira 2011[30] IG=44 CG=44	ADA guidelines HbA1c<7% SBP<130 mm Hg, DBP<80 mmHg Total cholesterol <200mg/dL HDL cholesterol<130mg/dL LDL cholesterol<100mg/dL	Change in proportion attaining goal: HbA1c 29.6% (P=.04) (OR 4.3 [1.2, 15.9]) SBP 31.8% LDL-C 18.2% Non-HDL-C 27.9%	Change in proportion attaining goal: HbA1c 11.9% SBP 14% (P=.10) LDL-C 13.6% (P=.53) Non-HDL-C 22.7% (P=.39)
Jameson 2010[36] IG=52 CG=51	HbA1C decreased by at least 1%	67.3% (35/52)	41.2% (21/51) (P=.02)
Johnson 2010[42] IG=222 CG=262	HbA1c <7% HbA1c <8% BP <130/80 mmHg LDL-C <100mg/dL BMI 18.5-24.9 kg/m^2	HbA1c <7% 43/222 (19.37%) (OR 4.04 [2.16, 7.56]) HbA1c< 8% 116/222 (52.25%) (OR 5.13 [2.22, 7.89]) BP <130/80 106/136 (77.94%) LDL-C 118/148 (79.73%) BMI 41/115 (35.65%)	HbA1c <7% 17/162 (6.49%) P<.001 HbA1c <8% 52/262 (19.85%) P<.001 BP<130/80 156/251 (62.15%) P=.002 LDL-C<100 85/182 (46.7%)P<.001 BMI 113/248 (45.56%) P=.08
Taveira 2010[31] IG=58 CG=51	ADA guidelines HbA1c<7% SBP<130 mm Hg, DBP<80 mmHg Non-HDL cholesterol<130mg/dL LDL cholesterol<100mg/dL	HbA1c 40.4% SBP 65.5% DBP 87.9% Non-HDL cholesterol 70.2% LDL cholesterol 77.2%	HbA1c 21.6% (P<.05) SBP 39.9% (P<.05) DBP 68.6% (P<.05) Non-HDL cholesterol 62.8% (P=NS) LDL cholesterol 77.5% (P=NS)
Fox 2009[47] IG (MTM participants)=255 CG1 (MTM non-participants)=56 CG2 (Not MTM eligible, CDC)=1,803	LDL-C <100mg/dL	69% (176/255)	CG1= 50% (28/56) CG2= 54.1% (976/1803) (P<.001)
Scott 2006[40] IG=64 CG=67	HbA1c <7% SBP <130 mmHg	HbA1c 67.2% (43/64) SBP 78% (50/64)	HbA1c 35.8% (24/67) (P=.05) SBP (numbers not reported) (P=.04)

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal (n/N)	
		Pharmacy component	Control
Odegard 2005[51] IG=43 CG=34	American Diabetes Association target for diabetes control (HbA1c <7%)	8%	13% (P=.69)
Shane-McWhorter 2005[41] IG=176 CG=176	HbA1c <7% SBP <130 mmHg DBP <80 mm Hg Total cholesterol <200mg/dL LDL<100 mg/dL TG <150mg/dL HDL >40mg/dL	HbA1c 58 (38.4%) SBP 66 (39.8%) DBP 65 (39.2%) TC 52 (61.9%) LDL 42 (53.2%) TG 28 (35.4%) HDL 41 (51.9%)	HbA1c 48 (27.7%) P=.04 SBP 74 (42.1%) P=.67 DBP 80 (45.5%) P=.24 TC 45 (47.4%) P=.13 LDL 28 (42.4%) P=.20 TG 26 (28.5%) P=.42 HDL 59 (66.3%) P=.06
Kelly 2000[44] IG=32 CG=16	HgA1c HbA1c <7% SBP <130mmHg DBP <85mmHG	HbA1c 31.3% (10/32) SBP 43.8% (14/32) DBP 65.6% (21/32)	HbA1c 6.3% (1/16) (P=.03) SBP 12.5% (2/16) (P=.01) DBP 62.5% (10/16) (P=.78)

ADA = American Diabetes Association; BP = blood pressure; CG = control group; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin; HDL(-C) = high-density lipoprotein (cholesterol); IG = intervention group; LDL(-C) = low-density lipoprotein (cholesterol); NR = not reported; SBP = systolic blood pressure; SMBG = self- monitored blood glucose; TC = total cholesterol; TG = triglycerides

[a] significant change from year before

[b] significantly different between groups

Table 26. Study and Intervention Characteristics – Dyslipidemia Studies

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Smith 2013[54] Retro Cohort Primary Care (VA)	Patients with uncontrolled LDL cholesterol based on NCEP/ ATPIII goal Maximum of 46 months (patients followed from index visit until LDL goal achieved or end of study period)	Inclusion: -patient seen in intervention or usual care (study) clinic -cholesterol-lowering medication changed or initiated during study period -random sample (~15%) chosen for study (225 in each group) Exclusion -index or final cholesterol values were missing	More effective and efficient lipid management compared to usual care Primary outcome: differences in mean final measured values of lipids and triglycerides between intervention and control cohorts	Clinical pharmacist, at least 1 year post-grad residency training	N=213 -Patients referred by clinician for further evaluation and adjustment of therapy -Pharmacists reviews results from laboratory tests and adjusted medications as necessary -Patient discharged from program when they reach individual NCEP/ATPIII goal *Mode/Frequency:* -patients seen by pharmacist for at least one visit -follow-up visits at 6- to 8-week intervals as needed	N=219 unmatched, groups randomly chosen from same population -Pharmacists provide drug information services and perform chart review for formulary management and cost-saving initiatives -Teaching clinic so patients followed more frequently (approx. 6- to 8-weeks) -No care management services	Physicians, nurse practitioners Pharmacists work with a group of practitioners to provide care management and drug information services
Miller 2008[55] Prospec-tive cohort Family medicine and other ambula-tory care (university -based)	Patients with dyslipidemia treated with atorvastatin 4 to 52 weeks (first fasting lipid panel after conversion to new statin regimen)	Inclusion: -enrolled in Colorado Indigent Care Program -diagnosis of dyslipidemia -treated with atorvastatin (prescribed by study clinic provider) Exclusion: -taking amiodarone, verapamil, cyclosporine, and/or gemfibrozil -history of transplantation or HIV -no fasting lipid panel before statin conversion -not adherent (based on refill history) with atorvastatin, or refused conversion	Improve outcomes following statin conversion Reduction in concentration of LDL and LDL goal attainment	Clinical pharmacy specialists and year-2 resident	N=30 Family medicine center patients: -Conducted individual medical review to identify goal -Reviewed patient LDL goal (NCEP ATP III); made therapeutic conversion to simvastatin, rosuvastatin, or ezetimibe-simvastatin (dose based on whether or not patient had achieved LDL goal on atorvastatin) *Mode/Frequency:* -Pharmacist did medication review, contacted patients to explain changes made -Patients asked to see PCP at 3 months (lipid panel, other tests)	N=87 unmatched Internal medicine, cardiology, and endocrinology clinic patients Usual care When refill request for atorvastatin received, pharmacy contacted provider to recommend equipotent conversion Recommendation was optional and final selection was made by provider	Pharmacist collaborated with prescribing physician to approve new regimen

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Mazzolini 2005[56] Retro cohort Outpatient clinics (VA)	Dyslipidemia Reviewed charts until reached goal of 115 patients in each group Followed at least 6 months after index visit	Inclusion: *Intervention group* -referred by primary care; referral is voluntary -randomly selected study patients from all attending lipid education class *Control group* -randomly selected from patients seen in primary care with diagnosis of dyslipidemia *Both groups* -diagnosis of dyslipidemia -≥3 visits with pharmacist or primary care -followed ≥6 months -enrolled in VA ≥1 year Exclusion: -documented non-compliance with appointments -TSH > 4.5 m IU/ml any time during study period	Compare outcomes with pharmacist-managed clinic vs care by other health professionals Primary: Absolute values and percentage changes in LDL; proportion attaining LDL goal	Clinical pharmacists with prescribing authority for all VA formulary lipid-lowering agents; perform all changes to lipid-lowering medications once patient enrolls in lipid clinic	N=115 -Assessed and treated dyslipidemia to achieve goals based on NCEP ATP III guidelines and recent recommendations -Education including treatment of dyslipidemia and therapeutic lifestyle modifications -Follow-up visits: discuss patient's lifestyle; changes in health status and current lipid profile reviewed; medication changes made if needed -Discharged if goal lipid levels maintained for 2 or more consecutive clinic visits *Mode/Frequency:* -Initial visit at clinic including class session -Scheduled for follow-up visits in the clinic	N=115 unmatched, randomly selected Usual care	Physicians, physician assistants, nurse practitioners Dietitians (education sessions)

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Straka 2005[57] CCT Staff-model HMO clinics	Coronary heart disease (CHD) At least 6 months follow-up after enrollment Post-study follow-up of 18 months to assess sustainability	Inclusion: -age ≥18 -CHD and LDL levels not at goal (<100 mg/dL) *Intervention group* included 1st 166 patients (of 359 eligible) who signed consent form (16 subsequently excluded) *Control group* included all eligible patients	Manage hyper-cholesterolemia in patients with CHD Primary: changes in magnitude of LDL, percentage achieving goal LDL levels	Clinical pharmacists	N=150 -Pharmacist and primary care provider cooperatively developed patient-specific care plan (implemented if physician approved and patient consented) -Pharmacist implemented plan: -prescribing and adjusting dosages -obtaining fasting lipid panel -evaluating and setting up all lipid panels -working through dosage titrations -communicating actions, recommendations, findings to physician -educating patients about risk/benefits of new or adjusted dosages -providing advice about aspirin, diet, weight loss, exercise -referring to other resources (smoking cessation, dietary counseling) *Mode/Frequency:* -Pharmacist met with PCP to come up with plan -Patients contacted by telephone to follow-up for tests, to notify them of changes, and for education -Lipid panel/liver tests at baseline and then every 6 weeks, after stabilizing liver tests every 3-6 months, fasting lipid panel annually	N=331 Usual care (no clinical pharmacist providing oversight)	-Pharmacist and primary care provider cooperatively developed patient-specific care plan (implemented if physician approved and patient consented) -Communicated actions, recommenda-tions, findings to physician

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Ellis 2000[58] RCT – IMPROVE substudy Primary care at 9 VA Medical Centers	Dyslipidemia 12 months	IMPROVE Inclusion: -high risk for drug-related adverse events (meeting 3+ of following a. ≥5 drugs in regimen, b. ≥12 doses/day, c. ≥4 drug changes in past year, d. ≥3 concurrent diseases, e. history of noncompliance, f. treatment with drugs requiring monitoring) -VAMC patient ≥12 months -expected to continue VAMC care -residence close to VAMC -working telephone SUB-STUDY: -diagnosis of dyslipidemia Exclusion: -seen in pharmacist-managed clinics in past 12 months -life expectancy <12 months -psychiatric diagnosis requiring services of mental health clinic -poor English -visually impaired	LDL < 100 mg/dl for secondary prevention in patients with coronary artery disease or diabetes LDL < 130 mg/dl for all others Primary outcome not specified	Ambulatory care clinical pharmacists	N=208 with dyslipidemia Pharmaceutical care in addition to usual medical care -Drug assessments -Adjustments to medications to improve care and disease control -Identify and prevent drug-related problems -Exact role varied depending on scope of practice (*eg,* adjust drug therapy, order lab tests) (NOTE: pharmacist intervention not limited to dyslipidemia) *Mode/Frequency:* -Initial visit -Follow-up at least 3 times for at least 12 months -Intervention continued until goals were met (patient-specific goals developed with physician and pharmacist)	N=229 with dyslipidemia Usual care	Patient goals developed with physician

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Bogden 1997[59] RCT University-affiliated primary care teaching clinic	High total cholesterol 6 months	Inclusion: -total cholesterol ≥ 240 mg/dL within 6 months before randomization Exclusion: -minors -patients unable to sign consent form	Lower cholesterol levels and meet NCEP goals (pharmacist and physician teamwork) Change in total cholesterol from baseline level	NR	N=50 -Recommendations to physicians on dosage, drug selection (*eg,* least costly regimen), monitoring -Meeting prior to PCP visit -medication history -answer questions -encourage compliance -review laboratory data *Mode/Frequency:* -30-minute meeting with patients before their physician visit -Clinic visits at 0 and 6 months, interim visits also occurred	N=50 Usual care (including access to pharmacy clerk at patient request)	Pharmacist gave recommenda-tions to physician
Konzem 1997[60] CCT Primary care (VA)	Patients with hypercholesterolemia 52 weeks	Inclusion: -Diagnosis of hyper-cholesterolemia -prescribed colestipol hydrochloride oral suspension -not presently receiving any other lipid-lowering drugs -fasting lipid profile within 1 month before starting colestipol	Enhance patient acceptance and compliance with therapy and improve outcomes Primary outcome not specified	Pharmacists who had received training on intervention tasks	N=17 (3 lost to follow-up) -Therapy managed by pharmacist and physician (referred by physician) -Pharmacist provided -education -titrated dosages -dietary analysis -Telephone contacts to encourage compliance and evaluate acceptance of regimen -Data collection at 26, 52 weeks *Mode/Frequency:* -Initial visit -Contacted patients by telephone 2, 4, and 6 weeks after initial visit -Follow-up visit at 8 weeks to evaluate lab results and acceptance	N=20 Usual care, provided by physician; received drug counseling (what agent is for, instructions for taking) but no other contact from pharmacist	Physicians

ACE = angiotensin converting enzyme; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CPCRS = Clinical Pharmacy Cardiac Risk Service; DRP = drug related problem; ED = emergency department; EF = ejection fraction; EMR = electronic medical record; ESRD = end stage renal disease; HbA1c = glycosylated hemoglobin; HF = heart failure; HTN = hypertension; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; QOL = quality of life; TSH = thyroid-stimulating hormone

Table 27. Drug-related Problems Outcomes – Dyslipidemia Studies

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Konzem 1997[60] IG=17 CG=20	NR	NR	NR	NR	NR	NR	Compliance 89% (9.2%) n=14	NR	NR	NR

CG = control group; IG = intervention group

Table 28. Mortality, Quality of Life, Access, and Patient Satisfaction Outcomes – Dyslipidemia Studies

Study; Intervention (n) Control (n)	All-cause mortality% (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
No studies reported								

CG = control group; IG = intervention group

Table 29. Healthcare Utilization and Cost Outcomes – Dyslipidemia Studies

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Smith 2013 IG=213[54] CG=219	Mean number of visits per patient 2.0 (1.3)	2.0 (1.3) P = .77	NR	NR	NR	NR	Mean number of interventions per patient (*eg*, medication changes) 1.1 (1.8)	0.7 (1.1) (P=.002)	NR	NR

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Miller 2008[55] IG=30 CG=87	NR	NR	NR	NR	NR	NR	Post-conversion change in potency Higher: 23% Equivalent: 70% Lower 7%	Higher: 16% Equivalent: 48% Lower: 36%	NR	NR
Mazzolini 2005[56] IG=115 CG=115	Annual visits 2.97	2.98 (P=.06)	NR	NR	NR	NR	Use of lipid-lowering agent 94% (108/115)	24% (28/115) (P<.0001)[a]	NR	NR
Straka 2005[57] IG=150 CG=331	NR	NR	NR	NR	NR	NR	Use of lipid lowering therapy Pre-intervention: 57% (86/150) Post: 78% (117/150)	Pre-intervention: 48% (158/331) Post: 44% (146/331) (P<.0001 between groups post-intervention)	NR	NR
Ellis 2000[58] IG=208 CG=229	Physician visits Baseline 769 12 months 799	Physician visits Baseline 850 12 months 925	NR	NR	NR	NR	NR	NR	Mean changes in costs from year before to year after randomization Total: $1583 Hospitalizations: $710 Clinic visits: $302 All drugs: $269	Total: $1213 Hospitaliza-tions: $670 Clinic visits: $372 All drugs: $106 All differences in change in mean (P>.05)

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Bogden 1997[59] IG=50 CG=50	Mean of 12 clinic visits	Mean of 9 visits (P<.05)	Reported frequencies of ER visits did not differ significantly between groups		NR	NR	27 medications started 21 medications discontinued 16 dose increases	NR	Mean medication charge in last month $11.40 decrease per patient from 1st month	$3.82 increase (P=NS)
Konzem 1997[60] IG=17 CG=20	NR	NR	NR	NR	NR	NR	Percent continuing colestipol 8 weeks: 80% 52 weeks: 65% Mean (std) dosage (g/day) at 8 weeks: 18 (4) 52 weeks: 13 (5)	Continuing 8 weeks: 70% 52 weeks: 40% (P<.05 at 52 weeks) Dosage 8 weeks: 10 (3) 52 weeks: 9 (2) (both P<.05) NOTE: discontinued because of side effects, noncompli-ance, and dissatisfac-tion	NR	NR

CG = control group; IG = intervention group
[a] Calculated P value (not reported in study)

Table 30. Goal Attainment Outcomes – Dyslipidemia Studies

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal (n/N)	
		Pharmacy component	Control
Smith 2013[54] IG=213 CG=219	Individually set LDL goals based on NCEP/ATP III guidelines	80.3% OR 2.6 (95% CI 1.6, 4.3), P<.001	65.3%
Miller 2008[55] IG=30 CG=87	LDL goal based on risk factors	Pre-conversion: 80% Post: 97% (P=.04, pre vs post)	Pre-conversion: 90% Post: 75% (P=.01, pre vs post)
Mazzolini 2005[56] IG=115 CG=115	LDL goal TC HDL TG	64.3% Change: 45.2% to 82.6% P<.001 43.5% to 23.5% P=.002 56.5% to 65.2% P=.224	15.7% (P<.001)
Straka 2005[57] IG=150 CG=331	LDL < 100 mg/dl	72% Difference remained significant after 18 months post-intervention follow-up	18% (P<.001)
Ellis 2000[58] IG=208 CG=229	LDL < 100 mg/dl	Baseline: 26% (23/89) Follow-up: 40% (49/124)	Baseline: 22% (24/107) Follow-up: 35% (40/116) P=.97 for difference between groups at end of study
Bogden 1997[59] IG=50 CG=50	LDL goals based on comorbid conditions and risk factors (< 160 mg/dL, < 130 mg/dL, or < 100 mg/dL)	Total Group: 43% (20/27) Goal of <160 or <130 mg/dL 38% (13/34) Goal of < 100 mg/dL 54% (7/13)	21% (10/47) (P<.05) 14% (5/36) (P<.05) 45% (5/11) (P>.05)
Konzem 1997[60] IG=17 CG=20	LDL goal at week 8 LDL goal at week 52	42% 29%	15% 5% (P<.05)

CG = control group; IG = intervention group; LDL = low-density lipoprotein; OR = odds ratio

Table 31. Study and Intervention Characteristics – Hypertension Studies

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Carter 2015[61] CAPTION cRCT 32 primary care offices	Uncontrolled hypertension (focus on minorities)	Randomized by office, office must have had an onsite clinical pharmacist Inclusion: -English or Spanish speaking -age >18 years -uncontrolled BP (>140/90mmHg or >130/80 mmHg for patients with DM or CKD) Exclusion: -current signs of hypertensive emergency (acute angina, stroke, or renal failure) -systolic >200mmHg or diastolic >114mmHg -history of MI, stroke, or angina (past 6 months) -systolic dysfunction (LVEF <35%) -GFR <20mL/min -cirrhosis -hepatitis B or C infection or laboratory abnormality in past 6 months -pregnancy -pulmonary hypertension or sleep apnea (unless treated) -life expectancy < 2 years -residence in nursing home or dementia -inability to give consent or impaired cognitive function	BP control Blood pressure control at 9 months	Clinical pharmacist	N=194 Brief intervention (9 months) N=207 Sustained intervention (24 months) Interventions were the same -Medical record reviewed by pharmacist -Structured interview -Medication history -Assessment of knowledge of BP medications, dosages, timing, potential side effects, barriers to adherence -Create care plan with recommendations for physician to adjust therapy and recommendations for patients for medication education, improving adherence, and strategies for lifestyle modification *Mode/Frequency:* -Phone call at 2 weeks -Structured face-to-face visits at baseline, 1,2, 4, 6, and 8 months with options for additional visits	N=224 Usual care: Pharmacists instructed to avoid intervention for study participants but could provide usual care curbside consultations if physicians specifically asked; control offices participated in an alternative distracter intervention for asthma	-Pharmacist created care plan; shared with physician who could accept, reject, or modify

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Zillich 2015[66] Retro-spective case-control Urban Midwest VA Medical Center, primary care clinics with PACT teamlets	HTN, referred to care manage-ment program 12 months	Cases: patients with HTN referred to care management program Controls: patients with HTN not referred to program	Evaluate pharmacists HTN care management program with PCMH Differences in systolic and diastolic BP levels at 6 and 12 months follow-up	Clinical pharmacists	N=465 Scope of practice allowed pharmacists to: -meet individually with patients -provide patient education -initiate, change, and discontinue medications *Mode/Frequency:* -Initial face-to-face visit with pharmacist -Patient discharged from program when BP goals attained -No information provided on mode or frequency of contacts after initial visit	N=1268 (Matched [maximum of 3:1] on physician, age, gender, diagnosis of DM and CKD, baseline systolic BP, number of HTN medications) Usual care	PCP referred patients to pharmacist
Hirsch 2014[69] RCT (pragmatic) University-based primary care clinic	Uncontrolled HTN 6 and 9 months	Inclusion: -age ≥18 years -diagnosis of HTN with most recent BP measurement ≥140/≥90 mm Hg (≥130/≥80 mm Hg for DM) -current treatment with ≥1 anti-HTN medication -continuous active status with the clinic (defined as having a record of at least 1 visit in the 6 months before screening) Exclusion: -did not meet provisions of the clinical collaborative-practice protocol	BP control Mean change in BP from baseline	Clinical with >1y of pharmacy practice residency training and >7y experience in ambulatory care	N=75 Medication-therapy management (MTM) -Pharmacist could initiate, change, or discontinue medication therapy for management of uncontrolled HTN -Assessed patient knowledge of HTN and current treatment -Reviewed treatment goals, self-monitoring behavior, medical and medication history -Helped patient set goals. -Follow-up - reviewed progress toward goals, lab values, and adherence Therapeutic decisions and timing of patients' laboratory testing and follow-up visits left to pharmacists' clinical opinion, in consultation with physician if needed *Mode/Frequency:* -4 30-minute pharmacist visits (baseline, 3, 6, & 9 months), independent of PCP visits, and other contacts (clinic or telephone) as needed for follow-up with pharmacist	N=91 Usual care	Internal medicine physician -visits documented in EMR and shared

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Magid 2013[70] RCT (pragmatic) HMO based primary care clinic	HTN with higher than recommended BP 6 months	Inclusion: -age 18 to 79 years -diagnosis of HTN - 2 most recent BP readings ≥140/≥90 mm Hg (≥130/≥80 mm Hg for DM or CKD) -prescribed ≤3 anti-HTN medications -had computer/internet access. Exclusion: -limited life expectancy -recent MI, stroke, percutaneous coronary intervention, or coronary artery bypass graft surgery -ESRD -not English speaking	BP control Proportion of patients who attained their goal BP at the 6-month clinic visit	Clinical	N=175 American Heart Association Heart360 Web-enabled home BP monitoring intervention -Educational materials -Pharmacist met with patient and reviewed medication regimen, home BP measurements and adherence to anti-HTN medications -Made medication adjustments/changes as needed -Counseled on lifestyle changes *Mode/Frequency:* -Baseline and 6 months visits plus weekly review of BP summary reports	N=173 Usual care PCP follow-up and educational materials	Primary care physician, medication changes communicated via EMR
Margolis 2013[62] RCT (cluster) HMO based primary care clinic	Uncontrolled HTN 12 months Plus 6 months post-intervention follow-up	Inclusion: -uncontrolled HTN (≥140/≥90 mm Hg or ≥130/≥80 mm Hg for DM or CKD) at 2 most recent primary care visits in previous year Exclusion: -stage 4/5 kidney disease or ratio of albumin to creatinine of ≥700 mg/g -acute coronary syndrome, coronary revascularization, or stroke ≤3 months -known secondary causes of HTN -NYHA class III or IV CHF -known left ventricular ejection fraction <30% -pregnant	BP control Proportion of patients who attained their goal BP	Trained clinical	N=228, 8 clinics Intervention patients received home BP telemonitors -Transmitted BP data to pharmacists; anti-hypertensive therapy adjusted accordingly -1 hour in-person visit: reviewed history, education -Patient given individualized home BP goal -Telephone visits (every 2-4 wks) -pharmacists emphasized lifestyle changes and medication adherence -assessed and adjusted anti-hypertension therapy (with algorithms) -managed adverse effects *Mode/Frequency:* -First 6 months: met every 2 weeks via telephone until BP control sustained for 6 weeks; then monthly visits -During intervention months 7 through 12, telephone visits occurred every 2 months	N=222, 8 clinics Usual care	Primary care physicians

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Magid 2011[67] RCT VA, City/ county, and HMO based primary care clinics	HTN 6 months	Inclusion: - HTN -taking ≤4 anti-HTN meds -elevations in 2 of 3 most recent electronic BP measurements (>140/>90 mm Hg; for patients with DM/CKD, >130/80 mm Hg)	BP control Proportion of patients who attained their goal BP and mean change in BP from baseline	Clinical	N=174 Clinical pharmacist management of HTN with physician oversight -Patient education -Counseling on healthy therapeutic lifestyle changes -Pharmacist practiced under pre-approved drug therapy management protocols -Pharmacists reviewed home BP measurements, adherence to meds -Made medication adjustments as needed *Mode/Frequency:* -Baseline and 6 months visits plus weekly review of BP summary reports; if essential HTN, average home readings >135/85 mm Hg triggered pharmacist intervention (>125/75 mm Hg if diabetes or CKD)	N=164 Usual care	Primary care physician, notified of changes via EMR/phone
Carter 2009[63] RCT (prospective cluster) Community-based family medicine residency program clinics	HTN 6 months	Inclusion: -age ≥21 years -essential HTN -taking 0-3 anti-HTN meds -if no DM: clinic systolic BP 140-179 mm Hg or clinic diastolic BP 90-109 mm Hg (130-179 mm Hg or 80-109 mm Hg with DM) Exclusion: -BP medication or dose change ≤4 weeks prior to base-line visit -BP >180/110 mm Hg -evidence of hypertensive urgency or emergency -recent MI or stroke (within 6 months before enrollment) -NYHA class III/IV CHF, unstable angina, renal/hepatic disease -life expectancy <3 years -dementia/cognitive impairment	BP control Change in guideline adherence scores, % of patients with controlled BP, difference in mean systolic and diastolic BPs	Clinical -Residency in primary care	N=192, 3 clinics Pharmacists were encouraged to: -Assess medications and BP at baseline and at 1 month, at 3 months, and more frequently if necessary -Pharmacists made recommendations consistent with national guidelines *Mode/Frequency:* -Baseline, 3, and 6 months -Pharmacists were encouraged to assess medications and BP more frequently if necessary	N=210, 3 clinics Usual care (Passive observation group (intervention sites only) n=191)	Physicians (and research nurses) -Collaboration on how to best implement intervention -Pharmacists almost always provided face-to-face recommenda-tions to PCP -Physician education if necessary -All therapy changes approved by physician

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Carter 2008[64] RCT prospective (cluster) University-based primary care clinics	HTN 9 months	Inclusion: -age 21-85 years -HTN: if no DM clinic BP 145-179 mm Hg/ 95-109 mm Hg (135-179 mm Hg or 85-109 mm Hg for patients with DM) Exclusion: -BP medication or dose change ≤4 weeks prior to baseline visit -enrollment in 24-hour BP monitoring consult service ≤ 6 months -stage 3 HTN (BP >180/110 mm Hg) -evidence of hypertensive urgency or emergency -recent MI or stroke (within 6 months before enrollment) -NYHA class III or IV CHF, unstable angina, serious renal or hepatic disease -poor prognosis (life expect. <3 years) -dementia or cognitive impairment	BP control Difference in mean systolic and diastolic BPs and proportion of patients with controlled BP	Clinical	N=101, 2 clinics Patient interview at baseline by clinical pharmacist -Assessed patient's regimen, suggested goal BP value, and provided recommendations to improve BP control -Primary focus of pharmacist was to address suboptimal medication regimens -Recommended adherence aids -Educated patients and/or taught them home monitoring -Made patient-specific recommendations -Recommend therapies consistent with JNC 7 guidelines *Mode/Frequency:* -Pharmacists encouraged to attend each clinic visit (2, 4, 6, and 8 months) and encouraged to initiate additional visits or telephone contact if BP remained uncontrolled	N=78, 3 clinics Usual care	Physicians (and nurses) -Pharmacist educated physician and made recommenda-tions -Pharmacists could not independently prescribe therapy; all changes approved by physician -Most recommenda-tions to physician performed face-to-face during patient visit; some physicians provided authority for pharmacists to make dosage changes and inform PCP immediately after visit

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Green 2008[71] Ralston 2014[74]* RCT Nonprofit, HMO-based primary care clinics *Sub-study with n=186 (intervention group), n=197 (control group – all home BP and Web)	HTN 12 months	Inclusion: -age 25-75 years -HTN diagnosis -taking antihypertensive meds -no diagnoses of DM, CVD or renal disease, or other serious conditions Eligible and willing patients were invited to 2 screening visits at their clinic. If mean diastolic BP (last 2 of 3 BP recordings, with the first measurement dropped) was between 90-109 mm Hg or mean systolic BP was between 140-199 mm Hg at both screening visits, participant was eligible for the study	BP control Difference in mean systolic and diastolic BPs and proportion of patients with controlled BP	Clinical	N=261 Pharmacist care plus home BP monitoring, and web training -1 planned telephone visit to obtain a more detailed medication history and review allergies, intolerances, and CV risk factors -Introduced patient to action plan, a template with 5 components: 1) instructions for home BP monitoring 2) list of current medications 3) ≥1 patient-selected lifestyle goal(s) from the list in the Group Health HTN pamphlet 4) recommended medication changes based on stepped medication protocols 5) follow-up plan -Planned communication occurred over web every 2 weeks until BP controlled -Responded to patients with specific recommendations (including medication changes) *Mode/Frequency:* -Baseline and 12 months -All planned communications occurred over web every 2 weeks until BP controlled and less often thereafter	1) N=258 Usual care 2) N=259 Home BP monitoring and web training only	Pharmacist communicated with physician, all clinical concerns or potential deviations from the medication protocol were referred back to PCP

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Hunt 2008[72] RCT Nonprofit integrated system, primary care clinics	HTN and uncontrolled blood pressure 12 months	Inclusion: -HTN and uncontrolled BP, -office visit within past 2 years (problem list entry of hypertension (ICD-9 of 410.*) -last systolic BP ≥160 mm Hg and/or a last diastolic BP ≥100 mm Hg) Exclusion: -no BP reading in chart in previous 2 years -attended a visit with a pharmacy practitioner in previous 6 months	BP control Difference in mean systolic and diastolic BPs	Clinical	N=230 Pharmacists: -Reviewed subjects' medications and lifestyle habits -Assessed vital signs -Screened for adverse drug reactions -Identified barriers to adherence -Provided education -Optimized anti-HTN regimen (titrating dose of existing medication, adding new agent, switching medication, or consolidating anti-HTN therapy) -Follow-up appointments as needed -Accessed patients' medical records to assist medication selection and dosing *Mode/Frequency:* -Baseline visit with pharmacist -Follow-up appointments as necessary	N=233 Usual care	Physician available to discuss HTN treatment plan/other medical issues as needed; notes from visit communicated via EMR
Borenstein 2003[73] RCT Community hospital	HTN uncontrolled 12 months	Inclusion: -age ≥18 years -capitated medical insurance -diagnosis code for HTN -uncontrolled HTN (>140/90 of <65 years old or >160/90 if >65 years old) based on last recorded measure(s) Exclusion: -advanced dementia, terminal illness, organ transplantation, or secondary hypertension -absence of recorded blood pressure measurements	BP control Difference in mean systolic and diastolic BPs	Clinical	N=98 -Pharmacists: -Determined BP -Collected patient assessments for adherence, potential drug side effects, and relevant patient habits (tobacco use, diet, and exercise), per JNC V guidelines -During clinic, pharmacists reviewed drug side effects and provided education regarding individualized dietary and lifestyle modifications -Called patient's physician/covering physician, with findings and made treatment recommendations in accordance with evidence-based treatment algorithm *Mode/Frequency:* -Follow-up visits every 2-4 weeks at discretion of pharmacist (as often as necessary until BP control achieved)	N=99 Usual care	Physician; physicians made all final treatment decisions

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Vivian 2002[68] RCT Veterans Affairs Medical Center	HTN 6 months	Inclusion: -stage 1, 2, or 3 hypertension as defined by JNC VI (>140 systolic or >90 diastolic) -age ≥18 -receiving anti-hypertension drug therapy -not receiving care at pharmacist-managed clinic Exclusion: -secondary cause of hypertension (CKD, renovascular disease, pheochromocytoma, Cushing's syndrome, and primary aldosteronism) -missed >3 appointments in last year -were in hypertensive crisis (systolic BP >210 mm Hg or diastolic BP >110 mm Hg) -NYHA class III or IV CHF, ESRD, psychiatric disorder, severe hepatic dysfunction, terminal cancer, or other condition with life expectancy to <1 year	BP control Difference in mean systolic and diastolic BPs and proportion of patients with controlled BP	Clinical	N=27 Pharmacist -Prescribing authority -Made appropriate drug therapy changes (in both drug selection and dosage) for blood pressure control in accordance with JNC VI -Did not make any changes in patients' other drugs that may adversely affect blood pressure (*eg,* venlafaxine, sibutramine) -Drug counseling provided at each visit (thorough discussion about side effects, recommended lifestyle changes, an assessment of compliance) *Mode/Frequency:* -Saw pharmacist 1 time/month	N=29 Usual care -Traditional pharmacist services (*eg,* distribution)	Not reported

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Okamoto 2001[75] RCT General medicine clinics within a managed care facility	HTN 6 months	Inclusion: -age ≥18 years -diagnosed with essential HTN -member of the managed care organization for ≥1 year -fill prescriptions at managed care organization's pharmacies -taking targeted anti-HTN drugs nifedipine, verapamil, captopril, diltiazem, clonidine, terazosin, propranolol, or lisinopril, or taking ≥3 prescription anti-HTN drugs Exclusion: -secondary HTN (secondary to drugs or comorbid diseases including but not limited to CKD, cancer, Cushing's syndrome, primary aldosteronism, or aortic coarctation) -significant end-organ disease (hospitalization likely within next few months) -baseline blood pressure > 200 mm Hg/105 mm Hg	BP control Difference in mean systolic and diastolic BPs, quality of life, costs	Clinical	N=164 -Pharmacist -informed patients that effort would be made to decrease number of drugs for HTN or alter therapy by administering more appropriate/less expensive drugs to achieve similar or improved BP control -determined most appropriate anti-HTN regimen for patient and ordered laboratory tests as needed -provided education on non-pharmacologic ways to control BP *Mode/Frequency:* -visits at baseline and 6m -pharmacist and physician could schedule additional appointments if necessary	N=166 Usual care Physician-managed	Not reported
Solomon 1998[23] Gourley 1998[24] RCT Veterans Affairs Medical Center and university medical center	HTN 6 months	Inclusion: -age ≥18 years -receiving dihyropyridine or dihyropyridine and diuretic therapy for HTN Exclusion: -symptomatic heart failure -taking any anti-HTN agent other than dihyropyridine -evidence of alcohol or drug abuse -participated in investigational drug trial within 30 days of enrollment	Evaluate effects of pharmacy care on humanistic outcomes Compliance, knowledge, health resource use, QoL, satisfaction with care	Clinical	N=63 Pharmacist care defined as -standardized patient assessment activities (physical assessment) -regularly scheduled therapeutic and educational interventions *Mode/Frequency:* -5 clinic visits, every 4 to 6 weeks	N=70 Usual care (traditional pharmacy care) (n=70)	Not reported

Author, year Study design Type of Clinic	Target Population Duration of Study/ Follow-up	Inclusion/Exclusion Criteria	Goal of Intervention Primary Outcome	Type of Pharmacist	Pharmacist Intervention	Comparator Intervention	Collaboration
Erickson 1997[65] CCT University medical center	HTN 5 months	Inclusion: -age ≥18 years -read and speak English -diagnosis of essential HTN (baseline diastolic > 90 mm Hg and/or systolic > 140 mm Hg) documented on their medical record, and be -taking a prescribed antihypertensive drug Exclusion: -secondary HTN (drug induced, pheochromocytoma, chronic renal disease or renovascular disease, Cushing's syndrome, primary aldosteronism, coarctation of the aorta)	BP control Primary outcome not specified	Clinical	N=40 -Reviewed medical records -Took drug history including current and previous prescription and nonprescription therapy and presence of side effects -Assessed patient-specific drug issues (*ie,* access to pharmacy services, concerns and beliefs about taking drugs), prescription drug coverage; compliance; patient knowledge about hypertension, lifestyle modification, and drug therapy -Consulted with physicians about potential or observed drug-related problems -Counseled patients regarding new or continued drug therapy; reinforcing the importance of lifestyle modification -Monitored drug therapy via interview and laboratory data -Taking and/or interpreting blood pressure measurements *Mode/Frequency:* -Regularly scheduled clinic visits during study period	N=40 Usual care Not matched	Not reported

BP = blood pressure; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; DM = diabetes mellitus; EMR= electronic medical record; ESRD = end-stage renal disease; HTN = hypertension; JNC V = Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure; MI = myocardial infarction; NYHA = New York Heart Association; PACT = patient-aligned care team; PCMH = patient-centered medical home; PCP = primary care provider; QoL= quality of life

Table 32. Drug-related Problems Outcomes – Hypertension Studies

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control
Carter 2015[61] IG=194 (Brief) IG=207 (Sustained) CG=224	NR	NR	NR	NR	NR	NR	NR	NR	No overall differences in the frequency of subjects reporting any serious adverse event across the 3 groups	
Zillich 2015[66] IG=465 CG=1,268	NR	NR	NR	NR	NR	NR	MPR at 12m All BP meds 0.71 (0.19) MPR >/=80% at 12m all BP meds 35%	0.71 (0.20) (P=.89) 32% (P=.69)	NR	NR
Hirsch 2014[69] IG=75 CG=91	Of patients with a drug problem: *Need for additional therapy* Baseline 42% (14/33) 6 months 58% (7/12) 9 months 25% (1/4) *Need for dose increase* Baseline 33% (11/33) 6 months 25% (3/12) 9 months 25% (1/4)	NR	NR	NR	NR	NR	Of patients with a drug problem: *Non-adherence:* Baseline 15% (5/33) 6 months 8% (1/12) 9 months 25% (1/4)	NR	Of patients with a drug problem: *Adverse drug reaction* Baseline 6% (2/33) 6 months 16% (2/12) 9 months 0	NR
Magid 2013[70] IG=175 CG=173	NR	NR	NR	NR	NR	NR	Mean MPR Baseline 0.86 6m 0.87 (P=.93) Adherence to home BP monitoring 30% (49/162)	NR	NR	NR

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control
Margolis 2013[62] IG=228 CG=222	NR	NR	NR	NR	NR	NR	6 months[a] 23% 12 months[a] 31% 18 months[a] 28%	6 months[a] 39% (P=.04) 12 months[a] 36% (P=.33) 18 months[a] 37% (P=.06)	Total: 49 events *Hypotension, dizziness, or loss of conscious:* 6 events *HTN related:* 1 event *Stroke:* 2 events *Atrial fibrillation:* 1 event *Angina:* 1 event	Total: 60 events *Allergic reactions attributed to HTN medicine:* 2 events *Hypotension, dizziness, or loss of conscious:* 1 event HTN-related: 4 events Stroke: 5 events *TIA:* 3 events *Atrial fibrillation:* 1 event *MI:* 1 event *Cardiac bypass surgery:* 2 events
Magid 2011[67] IG=174 CG=164	NR	NR	NR	NR	NR	NR	6 months[a] 30%	6 months[a] 31% (P=.93) *based on subset of 224 patients*	NR	NR
Carter 2009[63] IG=192 CG=210	NR	NR	NR	NR	NR	NR	Baseline 17% (SD 28%) 6 months 15% (SD 25%)	Baseline 19% (SD 22%) 6 months 15% (SD 21%) (P=.98)	NR	NR

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control
Carter 2008[64] IG=101 CG=78	NR	NR	NR	NR	NR	NR	Baseline 29% 9 months[a] 6%	Baseline 11% 9 months[a] 8% (P=.369)	Adverse event score[b] Baseline 28.8 9 months 22.2	Adverse event score[b] Baseline 26.5 9 months 18.3 (P=.135)
Green 2008[71] IG=261 Home BP and Web only CG=259 Usual care CG=258 Ralston 2014[74] (sub-study) IG=186 CG=197 Home BP and Web	NR	NR	NR	NR	NR	NR	Adherence at least 80% 176/186 (95%)	179/197 (91%) (P=.224) (Ralston 2014)	Nonfatal CV events 1% (3/261)	Nonfatal CV events Usual care <1% (2/258) Home/web only 1.5% (4/259) (Green 2008)
Hunt 2008[72] IG=230 CG=233	NR	NR	NR	NR	NR	NR	12 months[a] 33%	12 months[a] 31% (P=.77)	NR	NR
Vivian 2002[68] IG=27 CG=29	NR	NR	NR	NR	NR	NR	>90% of patients in both groups stated they took their drugs as directed by their health care professional and did not take more than prescribed (P=1.00) -Forgot to take drug ≥1x/wk IG: 68% CG: 48% (P=.252)		NR	NR
Okamoto 2001[75] IG=164 CG=166	NR	NR	NR	NR	NR	NR	NR	NR	None Reported	*Cardiac problems* 2 patients *Headache* 1 patient *Dizziness* 1 patient

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control	Pharmacy Component	Control
Solomon 1998 Gourley 1998[c] [23,24] IG=63 CG=70	Drug needed not prescribed 1.6% (4/255 problems identified by pharmacists) Drug not needed but prescribed 0.4% (1/255) Dose problem 3.5% (9/255)	NR	NR	NR	Risk of interaction 12.2% (31/255 problems identified by pharmacists)	NR	Patient compliance 0.23[d]	Patient compliance 0.61[d] (P<.05)	NR by group	NR by group

*All p-values versus control unless indicated. ARQ = Adverse reaction questionnaire; BP = blood pressure; CG = control group; CV = cardiovascular; IG = intervention group; MI = myocardial infarction; MPR = medication possession ratio; TIA = transient ischemic attacks

[a] Values reported are the inverse of adherence to hypertension medication

[b] Adverse reaction questionnaire included 47 questions of typical medication adverse effects; patient could rate the potential reaction as follows: 0 (not at all), 1 (a little bit), 2 (somewhat), 3 (quite a bit), or 4 (very much). The responses for each patient were summed (potential range, 0–188).

[c] Drug problems or needs identified by pharmacist were reported but there were no comparator data

[d] Mean sum score (1 point for every "yes" non-compliance item) based on a 4-item scale self-reported adherence measure

Table 33. Mortality, Quality of Life, Access, and Patient Satisfaction Outcomes – Hypertension Studies

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Hirsch 2014[69] IG=75 CG=91	NR	NR	NR	NR	NR	NR	Mean (SD) (0-100 scale with higher # = higher satisfaction) 6 months 92.4 (10.9); n=49 9 months 92.7 (11.0); n=44	NR
Magid 2013[70] IG=175 CG=173	NR	NR	NR	NR	NR	NR	*% very or completely satisfied with HTN care* 58% (102/175)	42% (73/173) P<.001[a]

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Margolis 2013[62] IG=228 CG=222	NR	NR	*SF-12 Physical* 0-100 mean (95% CI) Baseline 48.0 Change 6 months[b] -0.50 (-1.56, 0.56) 12 months[b] -0.84 (-2.0, 0.32) 18 months[b] -0.54 (-1.77, 0.69) *SF-12 Mental* Baseline 52.2 6 months[b] 0.25 (-0.88, 1.38) 12 months[b] -0.05 (-1.83, 0.78) 18 months[b] 1.51 (-0.18, 2.40)	*SF-12 Physical* 0-100, mean (95% CI) Baseline 47.3 Change 6 months[b] -1.17 (-2.26, 0.07) 12 months[b] -0.72 (-1.90, 0.45) 18 months[b] -0.82 (-2.09, 0.45) *SF-12 Mental* Baseline 51.2 6 months[b] 0.09 (-1.08, 1.26) 12 months[b] -0.78 (-2.11, 0.55) 18 months[b] 0.50 (-0.83, 1.84)	Can communicate with healthcare team: mean (95% CI) Baseline: 4.4 (4.2-4.5) Change 6m: 0.08 (-0.02, 0.18) 12m: -0.02 (-0.13, 0.1) 18m: 0.11 (-0.01, 0.21) Had problems getting needed care: Mean (95% CI) Baseline: 1.7 (1.5, 1.9) Change 6m 0.15 (-0.09, 0.39) 12m 0.15 (-0.15,0 .45) 18m 0.07 (-0.22, 0.35)	Can communicate with healthcare team: Mean (95% CI) Baseline: 4.4 (4.2-4.5) Change 6m: -0.06 (-0.16-0.04) 12m: 0.07 (-0.04-0.18) 18m: 0.09 (-0.01-0.2) Had problems getting needed care: Mean (95% CI) Baseline: 1.9 (1.6, 2.1) Change 6m 0.18 (-0.07, 0.43) 12m 0.04 (-0.26, 0.35) 18m 0.05 (-0.24, 0.34)	*CAHPS* 0-5[c] Overall rating of health care Baseline 4.3 (4.2, 4.4 Change 6 months[b] 0.27 (0.16, 0.39) 12 months[b] 0.22 (0.08, 0.35) 18 months[b] 0.26 (0.13, 0.38)	Baseline 4.3 (4.1, 4.4 Change 6 months[b] 0.11 (-0.01, 0.23) 12 months[b] 0.18 (0.14, 0.32) 18 months[b] 0.15 (0.03, 0.28)

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Green 2008[71] IG=261 Home BP and Web only CG=259 Usual care CG=258 Ralston 2014[74] IG=186 CG=197 (Home BP and Web)	<1% (1/261) Cardiac arrest	Usual care (0/258) Home/web only <1% (2/259) cancer	*SF-12 measures* 0-100, 100 highest *SF-12 General health* Baseline 67.1 (SD 20.4) 12 months 66.6 (22.2) *SF-12 Physical* Baseline 80.6 (SD 27) 12 months 81.0 (26.5) *SF-12 Emotional* Baseline 71.6 (SD 16.8) 12 months 71.7 (19.7)	*SF-12 Gen. health* Baseline 67.1 (SD 20.4) 12 months Usual care 66.7 (20.4) Home/web only 66.6 (20.9) *SF-12 Physical* Baseline 80.6 (SD 27) 12 months Usual care 78.1 (27.7) Home/web only 77.7 (30.3) *SF-12 Emotional* Baseline 71.6 (SD 16.8) 12 months Usual care 71.5 (17.7) Home/web only 72.1 (16.8)	NR	NR	*CAHPS* 0-10[c] Baseline 7.9 (SD 1.5) 12 months 8.3 (1.4) PACIC Overall Mean (SD) 3.3 (0.8)	Baseline 7.9 (SD 1.5) 12 months Usual care 8.1 (1.5) Home/web only 8.1 (1.5) (Green 2008) 2.5 (0.9) (P<.001) (Ralston 2014)
Hunt 2008[72] IG=230 CG=233	NR	NR	*MOS SF-36* *Physical* 41 *Mental* 45 *General Health* 44	*Physical* 42 (P=.12) *Mental* 44 (P=.16) *General Health* 42 (P=.01)	NR	NR	Overall satisfaction 8.6	8.5 (P=.75)
Vivian 2002[68] IG=27 CG=29	NR	NR	SF-36 No statistically significant differences were noted between the 2 groups from baseline to end of study		NR	NR	Very satisfied with pharmacy services 88% (23/26)	68% (18/27) (P=.098)

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Okamoto 2001[75] IG=164 CG=166	NR	NR	SF-36 Only statistically significant difference at end of study was found in the role-physical domain. Scores were significantly higher (P=0.03) in the Intervention group (78.5 vs. 70.7). No differences between groups for any other scores		NR	NR	NR	NR
Solomon 1998 Gourley 1998[23,24] IG=63 CG=70	NR	NR	No statistically significant differences were noted between the 2 groups on QoL items		NR	NR	Greater satisfaction in the intervention group. Intervention group provided more positive responses (significant differences in 8/10 items from the Pharmaceutical Care Questionnaire) about their pharmacists compared with controls	
Erickson 1997[65] IG=40 CG=40	NR	NR	Groups similar for SF-36 Health Survey scores		NR	NR	NR	NR

CAHPS = Consumer Assessment of Healthcare Providers and Systems survey; CG = control group; IG = intervention group; PACIC = Patient Assessment of Chronic Illness Care; QoL = quality of life; SF-36 = Short-Form 36

[a] All p-values versus control unless indicated

[b] Change from baseline (95% CI)

[c] 0 worst, 5 best

Table 34. Healthcare Utilization and Cost Outcomes – Hypertension Studies

Study; Intervention (n) Control (n)	Office visits (means (SD) unless otherwise indicated)		Urgent care or / Emergency room (ER) (means (SD) unless otherwise indicated)		Hospitalization (means (SD) unless otherwise indicated)		Medications (means (SD) unless otherwise indicated)		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Carter 2015[61] IG=194 (Brief) IG=207 (Sustained) CG=224	NR	NR	NR	NR	NR	NR	Dose increases or med additions First 9 months Brief: 3.1 (3.2) Sustained: 2.7 (3.1) At 12 months Sustained: 0.3 (0.8) At 18 months Sustained: 0.4 (1.2) At 24 months Sustained: 0.3 (0.9)	0.7 (1.0) (P<.001) 0.1 (0.5) (P=.25) 0.3 (0.7) (P=.31) 0.2 (0.5) (P=.21)	NR	NR
Zillich 2015[66] IG=465 CG=1,268	NR	NR	NR	NR	NR	NR	Medication Changes during 12 month follow-up: 4 types of BP meds had more changes (P<.01) in case group; 3 types of med plus "others" were non-significant	NR	NR	NR
Hirsch 2014[69] IG=75 CG=91	PCP visits Mean (SD) 1.8 (1.5) PC and pharmacy 4.4 (1.9)	PCP visits Mean (SD) 4.2 (1.0) (P<.001)[a] PC and pharmacy 4.2 (1.0) (P=.38)	NR	NR	NR	NR	NR	NR	NR	NR

Study; Intervention (n) Control (n)	Office visits (means (SD) unless otherwise indicated)		Urgent care or / Emergency room (ER) (means (SD) unless otherwise indicated)		Hospitalization (means (SD) unless otherwise indicated)		Medications (means (SD) unless otherwise indicated)		Costs or Other (describe)	
	Pharmacy component	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**
Magid 2013[70] IG=175 CG=173	Mean (SD) 3.3 (2.5); n=162	3.1 (2.3); n=164 (P=.16)	Mean(SD) 0.04 (0.19) n=162	0.05 (0.23) n=164 (P=.44)	Mean (SD) 0.03 (0.17) n=162	0.04 (0.20); n=164 (P=.57)	*No medication* 4% (6/162) *≥1 dose increase* 43% (69/162) *≥1 medications added* 70% (113/162)	*No medication* 9% (15/164) (P=.05) *≥1 dose increase* 12% (20/164) (P<.001) *≥1 medications added* 25% (41/164) (P<.001)	NR	NR
Margolis 2013[62] IG=228 CG=222	Pharmacist visits: 11.4 (SD 3.9)	NR	NR	NR	non-CV hospital-izations noted as most common adverse event out of n=49 events	non-CV hospital-izations noted as most common adverse event out of n=60 events	*Prescribed any HTN medication* Baseline 77% Change 6 months[b] 17% (13, 20) 12 months[b] 18% (13, 21) 18 months[b] 18% (14, 21); At months 6, 12, 18 95% were on HTN medication	Baseline 73% Change 6 months[b] 6% (-2, 13) (P<.01) 12 months[b] 7% (-0.8, 14) (P<.01) 18 months[b] 8% (-0.3, 14) (P<.05) At months 6, 12, 18 79-81% were on HTN medication	Direct program costs $1045 over the 12-month period	NR
Magid 2011[67] IG=174 CG=164	NR	NR	NR	NR	NR	NR	*# HTN med. classes* Baseline 2.1 Change 6 months[b] 0.3 *Intensity of HTN med. regimen[c]* Baseline 3.2 6 months[b] 0.6 (P=.008)	*# HTN med. classes* Baseline 2.1 Change 6 months[a] 0.1 (P=.05) *Intensity of HTN med. regimen[c]* Baseline 3.3 6 months[b] 0.2 (P=.008)	NR	NR

Study; Intervention (n) Control (n)	Office visits (means (SD) unless otherwise indicated)		Urgent care or / Emergency room (ER) (means (SD) unless otherwise indicated)		Hospitalization (means (SD) unless otherwise indicated)		Medications (means (SD) unless otherwise indicated)		Costs or Other (describe)	
	Pharmacy component	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**
Carter 2009[63] IG=192 CG=210	NR	NR	NR	NR	NR	NR	*Mean increase in # HTN meds. from baseline* 1.1 *# of HTN meds.* Baseline 1.3 6 months 2.4 (1.1)	*Mean increase in # HTN meds. from baseline* 0.3 (P<.001) *# of HTN meds.* Baseline 1.9 6 months 2.2 (1.1) (P=.22)	NR	NR
Carter 2008[64] IG=101 CG=78	NR	NR	NR	NR	NR	NR	*# HTN meds.* Baseline 1.5 9 months 2.4 (0.9)	*# HTN meds.* Baseline 1.4 9 months 1.9 (1.0) (P=.003)	NR	NR
Green 2008[71] IG=261 Home BP and Web only CG=259 Usual care CG=258	PC visits 3.2 between groups Modest significant decrease in % of patients with office visits to specialist in the intervention group (P=.04) vs. other groups	PC visits Usual care 3.2 Home/web only 3.0 P=NS	NS between groups		NS between groups		*# HTN med. classes* Baseline 1.64 12 months 2.16 (0.93) (P<.001) compared to all controls *Aspirin use* Baseline 49% 12 months 67% (149/222)	*# HTN med. classes* Baseline 1.64 12 months Usual care 1.69 (0.85); Home/web only 1.94 (0.91) *Aspirin use* Baseline 49% 12 months Usual care 53% (124/234) Home/web only 56% (131/234)	NR	NR

Study; Intervention (n) Control (n)	Office visits (means (SD) unless otherwise indicated)		Urgent care or / Emergency room (ER) (means (SD) unless otherwise indicated)		Hospitalization (means (SD) unless otherwise indicated)		Medications (means (SD) unless otherwise indicated)		Costs or Other (describe)	
	Pharmacy component	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**
Hunt 2008[72] IG=230 CG=233	PCP 3.2 (2.7); n=142 Total 7.2 (3.3) PC-HTN 1.8 (1.7) Total-HTN 5.8 (2.6)	PCP 4.7 (3.1); n=130 (P<.0001) Total 4.9 (3.3) (P<.0001) PC-HTN 2.9 (2.2) (P<.0001) Total-HTN 3.1 (2.4) (P<.0001)	NR	NR	NR	NR	*# HTN meds.* Mean (SD) 12 months 2.7 (1.2); n=142	*# HTN meds.* 12 months 2.4 (1.1); n=130 (P=.02)	*Use of generic anti-HTN agent* 51%	*Use of generic anti-HTN agent* 40% (P=.008)
Borenstein 2003[73] IG=98 CG=99	PC visits 3.4 Provider and pharmacy 8.0	PC visits 6.0 (P<.01) Provider and pharmacy 6.6 (P=.06)	NR	NR	NR	NR	*Patients receiving at least one first-line anti-HTN agent* Baseline 68% 12 months 80% (78/98) Change (P=.02)	*Patients receiving at least one first-line anti-HTN agent* Baseline 60% 12 months 70% (69/99) Change (P=.02)	*Average provider visit costs/patient* $160 *Increase in drug costs from baseline* $11.31	*Average provider visit costs/patient* $195 (P=.04) *Increase in drug costs from baseline* $4.25 (P=.12)
Vivian 2002[68] IG=27 CG=29	77% (20/27) had ≥1 appointment with physician	63% (17/29) had appointment with PCP (P=0.372).	NR	NR	NR	NR	ACEI 69 (18/26) NS for all other HTN meds	ACEI 96 (26/27) (P=.052) NS for all other HTN meds	NR	NR

Study; Intervention (n) Control (n)	Office visits (means (SD) unless otherwise indicated)		Urgent care or / Emergency room (ER) (means (SD) unless otherwise indicated)		Hospitalization (means (SD) unless otherwise indicated)		Medications (means (SD) unless otherwise indicated)		Costs or Other (describe)	
	Pharmacy component	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**	**Pharmacy component**	**Control**
Okamoto 2001[75] IG=164 CG=166	Clinic visits 5.25	Clinic visits 1.41 (P<.001)	None	4 patients	No patient hospitalized during the study for reasons related to BP		*# HTN meds.* Baseline 2.18 6 months 2.12	*# HTN meds.* Baseline 2.06 (P=.33) 6 months 2.2 (P=.67)	*Drug costs/pt* $112 ($153) *Clinic visit costs* $131 ($59) *Total cost/pt* $243 ($169)	*Drug costs/pt* $149 ($230) (P=.08) *Clinic visit costs* $74 ($89) (P<.001) *Total cost/pt* $233 ($267) (P=.71)
Erickson 1997[65] IG=40 CG=40	Clinic visits 4.1	Clinic visits 3.5 (P=.06)	NR	NR	NR	NR	Number of antihypertensive therapies prescribed per person similar between groups		NR	NR

ACEI = Angiotensin-converting enzyme inhibitor; CG = control group; CV cardiovascular; IG = intervention group; PC = primary care; PCP = primary care physician; pt = patient; SD = standard deviation

[a] All p-values versus control unless indicated

[b] Change from baseline (95% CI)

[c] Intensity of hypertension medication regimen was based on patient report of medication regimen (specific medication and dosage) with confirmation by reviewing the pharmacy list available through the site's electronic medical record or the pill bottles that patients brought to the visits. For each patient, an average intensity score was derived based on the sum of the medication intensity score divided by the number of antihypertensive medications prescribed.

Table 35. Goal Attainment Outcomes – Hypertension Studies

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal % (n/N)	
		Pharmacy component	Control
Carter 2015[61] IG=194 (Brief) IG=207 (Sustained) CG=224	BP <140/90 mmHg or <130/80 mmHg for patients with DM or CKD	9 months: 43% in intervention groups	9 months: 34% OR 1.57 (0.99, 2.50) (P=.059)
Zillich 2015[66] IG=465 CG=1,268	BP <130/80 mmHg (DM or CKD) BP <140/90 mmHg (Other)	Baseline: 35% 6m: 57% 12m: 64%	Baseline: 49% (P<.0001) 6month: 57% OR 1.1 (0.9-1.3) (P=.28) 12month: 60% OR 1.3 (1.1-1.6) (P=<.01)
Hirsch 2014[69] IG=75 CG=91	BP goal <140/<90 mm Hg; <130/<80 mm 41Hg with comorbid diabetes	Baseline 53% (40/75) 6 months 81% (60/74) 9 months 70% (50/71)	Baseline 46% (41/89) 6 months 44% (40/91) (P<.001) 9 months 52% (47/91) (P<.02)
Magid 2013[70] IG=175 CG=173	BP goal <140/<90 mm Hg; < 130/<80 mm Hg with comorbid diabetes or CKD	Overall: 6 m 54% (95/175) DM/CKD: 6 m 52% (42/81)	6 months, Overall 35% (61/173) 6 months, DM/CKD 22% (19/88) (P<.05)
Margolis 2013[62] IG=228 CG=222	BP goal <140/<90 mm Hg; <130/<80 mm Hg with comorbid diabetes or CKD	6 months 72% (148/206) 12 months 71% (141/198) 18 months 72% (135/188) 51% for patients attending all clinic visits at 6, 12,and 18 months Differential change from baseline for patients attending all clinic visits (95% CI) 29.6 (13.1, 46.0)	6 months 45% (89/197) (P<.001) 12 months 53% (102/193) (P=.005) 18 months 57% (104/182) (P=.003) 21% for patients attending all clinic visits at 6, 12,and 18 months
Magid 2011[67] IG=174 CG=164	BP goal <140/<90 mm Hg; <130/<80 mmHg with comorbid diabetes or CKD	6 months 36% (49/136)	6 months 35% (51/145) (P=.89)
Carter 2009[63] IG=192 CG=210	BP control was <140/90 mm Hg; <130/ 80 mm Hg with comorbid diabetes or CKD	6 months 64% (122/191) 6 months, non-diabetics 69% 6 months, diabetics 46%	6 months 30% (63/210) (P<.001) 6 months, non-diabetics 32% (P<.001) 6 months, diabetics 26% (P=.003)
Carter 2008[64] IG=101 CG=78	BP control was <140/90 mm Hg; <130/ 80 mm Hg with comorbid diabetes or CKD	9 months, Overall 89% (90/101); 9 months, non-diabetics 91% 9 months, diabetics 82%	9 months, Overall 53% (41/78); 9 months, non-diabetics 63% 9 months, diabetics 24% (P<.001)

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal % (n/N)	
		Pharmacy component	Control
Green 2008[71] IG=261 Home BP and Web only CG=259 Usual care CG=258	BP goal <140/<90 mm Hg	12 months 56% (133/237) (95% CI 49, 62%) P<.01 Patients With Systolic BP at Baseline ≥160 mm Hg 54% (28/52) (95% CI 40, 67%) P<.01	12 months Usual care 31% (77/247) (95% CI 25, 37%) Home/web only 36% (89/246) (95% CI 30, 42%) Patients With Systolic BP at Baseline ≥160 mm Hg Usual care 20% (10/51) (95% CI 11, 33%) Home/web only 26% (12/47) (95% CI 15, 40%)
Hunt 2008[72] IG=230 CG=233	Target BP was <140/90 mm Hg	12 months, last study visit 62% (88/142)	12 months, last study visit 44% (57/130) (P=.003)
Borenstein 2003[73] IG=98 CG=99	BP goal was <140/90 mm Hg for patients < 65 years of age; <160/90 mm Hg for patients ≥65 years of age	12 months 60% (59/98)	12 months 43% (42/98) (P=.02)
Vivian 2002[68] IG=27 CG=29	BP below140/90 mm Hg	6 months 81% (21/26)	6 months 30% (8/27) (P=.001)
Erickson 1997[65] IG=40 CG=40	BP goal ≤140/≤90 mm Hg	5 months 45% (18/40)	5 months 30% (12/40) (P=.17)

CG = control group; IG = intervention group; DM = diabetes mellitus; CKD = chronic kidney disease; NR=not reported; OR = odds ratio

Table 36. Study and Intervention Characteristics – Polypharmacy/High Risk Studies

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Lee 2006[77] FAME Cohort (phase 1) followed by RCT (phase 2) Outpatient general medicine service and Armed Forces Retirement Home (both Walter Reed Army Medical Center)	Older patients taking multiple medications 14 months 3 phases: -run-in phase: (n=200) 2 month run-in with no intervention; baseline adherence, BP, LDL determined -phase 1: (n=174) 6 month cohort, all patients received comprehensive program -Phase 2: (n=159) 6 month RCT (continuation of program or usual care)	Inclusion: -age 65 or older -taking at least 4 chronic medications per day Exclusion: -did not live independently (*ie*, nursing home or assisted living excluded) -serious medical conditions such that 1-year survival was unlikely	For RCT – determine maintenance of medication adherence after withdrawal of intervention Primary outcome: persistence of medication adherence	Clinical pharmacists	N=83 for RCT -Individualized medication education -Dispensing of medications in blister pack adherence aid -Follow-up every 2 months *Mode/Frequency:* -Run-in phase: initial visit -First phase: regular follow-up with clinical pharmacists every 2 months	N=76 for RCT Pre-study medication provision (no education, no blister packs)	Not reported

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Taylor, 2003[78] RCT Community-based primary care (Family medicine) clinics affiliated with academic center (rural, high-poverty)	Adults at high risk for medication-related adverse events 12 months	Inclusion: -age ≥18 yrs -receive care at participating clinics -3 or more of these risk factors: a. 5 or more meds b. 12 or more doses/day c. 4 or more med changes past year d. 3 or more concurrent diseases e. history of medication non-compliance, f. drugs requiring therapeutic monitoring Exclusion: -cognitive impairment -history of missed office visits -scheduling conflicts -life expectancy < 1 year	Determine effect of pharmaceutical care on prevention, detection, and resolution of drug-related problems in high-risk patients in a rural community Primary outcome not specified	Clinical pharmacist	N=33 Usual medical care plus: -20-minute meeting with pharmacist before PCP visit -Evaluate therapy indication, effectiveness, dosage; correct/give practical directions; assess drug interactions, therapeutic duplication, duration of treatment, untreated indications, and expense -Review medical record for med-related problems -Chart review - ensure drugs and allergies documented -History to determine compliance; check for complications of therapies -Comprehensive individualized patient education (review of disease, importance of lifestyle modifications, drug info) -Monitor patients' responses to drugs -Attempt to improve compliance through simplified dosing, teaching techniques like peak flow meter use, inhaler use, glucometer use, pill boxes *Mode/Frequency:* -20-minute meeting with pharmacist -Saw patients during follow-up visits	N=36 Usual medical care (no pharmacist intervention)	Therapeutic recommendations communicated to physicians orally or written notes

Author, year Study design Type of Clinic	Target Population Duration of study/ follow-up	Inclusion/ Exclusion Criteria	Goal of Intervention Primary Outcome	Type of pharmacist	Pharmacist Intervention	Comparator intervention	Collaboration
Malone et al, 2000 and 2001[79,80] RCT VA Medical Center primary care clinics	Adult ambulatory care patients at high risk for drug-related problems 12 months	Inclusion: -VAMC patient for ≥12 months, ongoing -3 or more of: a. 5 or more meds b. 12 or more doses/day c. 4 or more med changes past yr d. 3 or more concurrent diseases e. h/o med non-compliance f. drugs requiring therapeutic monitoring Exclusion: -participated in pharmacist-managed clinics past year -life expectancy <12 mo -psychiatry care -non-English speaker -visually impaired	"determine if clinical pharmacists could affect economic resource use and humanistic outcomes in a population of veterans identified to be at high risk to experience a medication-related problem" -economic Costs -HRQOL -patient satisfaction	Clinical pharmacist	N=523 -Pharmacists practiced within scope of practice of respective VAMC -Medical records reviewed and patients interviewed to optimize medication therapy -Assess appropriateness of medication therapy -Physical assessments, (*eg*, BP) -Establish goals of medication therapy -Assess medication compliance -Conduct in-office laboratory tests (*eg*, finger stick blood glucose) -Identify non-treated disease states that may benefit from pharmacological therapy -Check for drug interactions -Monitor meds for therapeutic effect and toxicity by requesting laboratory tests -Patient education -Refer patients to primary care physicians, specialists, and other health care providers -Depending on site and scope of practice, start, stop, or change medication therapy *Mode/Frequency:* -At least 3 visits with clinical pharmacist (most face-to-face, few telephone)	N=531 Primary care with physician; no pharmacist contact	"clinical pharmacists worked with physicians and other health care providers"

BP = blood pressure; ER = emergency room; h/o=history of; HRQOL = health related quality of life; LDL = low density lipoprotein cholesterol; MAI = medication appropriateness index; PCP = primary care provider; RCT = randomized controlled trial; VAMC = Veterans Affairs Medical Center

Table 37. Drug-related Problems Outcomes – Polypharmacy/High Risk Studies

Study Intervention (n) Control (n)	Inappropriate dosage/prescription or omission % (n/N)		Ineffectiveness% (n/N)		Drug-drug or drug-disease interaction (*describe*) % (n/N)		Non-adherence to prescribed regimen % (n/N)		Clinical/adverse events % (n/N)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Lee 2006[77] IG=83 CG=73	NR	NR	NR	NR	NR	NR	Mean (SD) adherence at end of RCT 95.5% (7.7%)	69.1% (16.4%) (P<.001)	NR	NR
Taylor 2003[78] IG=33 CG=36	Percent of prescriptions that were inappropriate *Inappropriate dosage:* Baseline: 63.3% (133/210 prescriptions) 12 months: 12.9% (20/155 prescriptions) *Inappropriate indication:* Baseline: 33.3% (70/210 prescriptions) 12 months 16.2% (25/155 prescriptions)	*Inappropriate dosage:* Baseline: 62.3% (129/207) 12 months: 63.8% (143/224) (P=NR) *Inappropriate indication:* Baseline: 46.8% (97/207) 12 months: 48.2% (108/224) (P=NR)	Baseline: 29.1% (61/210 prescriptions 12 months: 13.6% (21/155)	Baseline: 44.9% (93/207 prescriptions) 12 months: 44.6% (100/224) (P=NR)	Drug-drug Baseline: 22.9% (48/210 prescriptions) 12 months: 5.8% (9/155) Drug-disease Baseline: 18.6% (39/210) 12 months: 9.0% (14/155)	Drug-drug Baseline: 17.9% (37/207 prescriptions) 12 months: 22.8% (51/224) (P=NR) Drug-disease Baseline: 21.3% (44/207) 12 months: 19.6% (44/224) (P=NR)	Mean compliance 12 months 100%	Mean compliance (SD) 88.9 (6.3%) (P=.115)	Patients with at least one “medication misadventure” 12 months: 2.8% (4/33)	3.0% (3/36) (P=.73)

CG = comparison group; IG = intervention group; NR = not reported; SD = standard deviation

Table 38. Mortality, Quality of Life, Access, and Patient Satisfaction Outcomes – Polypharmacy/High Risk Studies

Study; Intervention (n) Control (n)	All-cause mortality % (n/N)		Health-related quality of life (*describe*)		Access to care (*describe*)		Patient satisfaction with care (*describe*)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Taylor 2003[78] IG=33 CG=36	NR	NR	SF-36, groups similar (P values not reported)		NR	NR	Pharmacy related satisfaction (reporting unclear) 81.9 (4.8)	89 (6.2) (P=.000)
Malone 2000, Malone 2001[79,80] IG=523 CG=531 randomized; 447 and 484 completed	NR	NR	SF-36, No clinically meaningful effect on HRQOL but evidence to suggest a dose-response relationship.		NR	NR	There was no difference in patient satisfaction between groups at baseline or over time.	

CG = comparison group; HRQOL = health-related quality of life; IG = intervention group; NR = not reported; SD = standard deviation; SF-36 = Short-form 36

Table 39. Healthcare Utilization and Cost Outcomes – Polypharmacy/High Risk Studies

Study; Intervention (n) Control (n)	Office visits		Urgent care visits/ Emergency room (ER) visits		Hospitalizations		Medications		Costs or Other (describe)	
	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control	Pharmacy component	Control
Lee 2006[77] IG=83 CG=73	NR	NR	NR	NR	NR	NR	Mean number of antihyper-tensives used 2.6 (1.23)	2.61 (1.14) (P=.93)	NR	NR
Taylor 2003[78] IG=33 CG=36	NR	NR	4/33 (total) Change from previous 12 months: -12	6/36 (total) Change from previous 12 months: 0 (P=.044)	2/33 (total) Change in hospitaliza-tions from previous 12 months: -22	11/36 (total) Change in hospitaliza-tions from previous 12 months: 0 (P=.003)	Number of prescribed medications mean (SD) at 12 months: 4.7 (2.0)	Number of prescribed medications mean (SD) at 12 months: 6.2 (2.0) (P=.002)	Drug is not least expensive of options Baseline: 50% (105/210 prescriptions) 12 months: 38.7% (60/155)	Baseline: 62.3% (129/207) 12 months: 60.3% (135/224) (P=NR)
Malone 2000, Malone 2001[79,80] IG=523 CG=531 randomized; 447 and 484 completed	Before: mean (SD) 21.7 (21.0) After: 26.3 (20.8) Mean increase 4.8	Before: mean 20.6 (17.2) After: 23.4 (20.5) Mean increase 2.8 (P=.003)	NR	NR	Before: 0.34 (0.78) After: 0.53 (0.98) Mean increase 0.13	Before: 0.36 (0.81) After: 0.57 (1.20) Mean increase 0.19 (P=.29)	Before: Drug fills: 56.9 (40.0) Mean increase 5.6	Before Drug fills: 53.2 (34.5) Mean increase 4.0 (P=.12)	Mean cost (all costs: clinic visits, drug, lab, and hospitaliza-tions) baseline: $4,927 After: $5,947 Mean increase $1,020	Mean cost baseline $4,419 After $5,732 Mean increase $1,313 (P=.06)

CG = comparison group; IG = intervention group; NR = not reported; SD = standard deviation

Table 40. Goal Attainment Outcomes – Polypharmacy/High Risk Studies

Study; Intervention (n) Control (n)	Patient Goal Attainment definition	Percentage of patients attaining goal (n/N)	
		Pharmacy component	Control
Lee 2006[77] IG=83 CG=73	Medication adherence > 80% at end of RCT	97% (75/77)	22% (15/69) (P<.001)
Taylor 2003[78] IG=33 CG=36	Hypertension (goal ≤ 140/90 mmHg, or ≤135/80mmHg if diabetic)	91.7% (22/24)	27.6% (8/29) (P<.005)
	Diabetes (HbA1c ≤7.5%)	100% (13/13)	26.7% (5/16) (P<.005)
	Dyslipidemia (ATP III guidelines)	77.8% (14/19)	5.9% (1/19) (P<.005)
	Anticoagulation (INR 2-3)	100% (4/4)	16.7% (1/6) (P=NS)

ATP III = Adult Treatment Panel III; CG = comparison group; IG = intervention group; INR = International Normalized Ratio; NR = not reported; NS = not statistically significant; RCT = randomized controlled trial

APPENDIX D. RISK OF BIAS TABLES

Table 1. Risk of Bias for Cardiovascular Disease, Dyslipidemia, Chronic Obstructive Pulmonary Disease, and Chronic Kidney Disease Studies

Author, Year	Randomized?	Sequence Generation	Allocation Concealment	Risk of Bias from Confounding (non-randomized)	Blinding	Incomplete Outcome Reporting	Selective Reporting	Overall
Cardiovascular Disease or Risk Factors for Cardiovascular Disease								
Taveira 2014[11]	Y	unclear	unclear		unclear	low	low	Medium
Irons 2012[12]	N		high	high	unclear	low	low	High
Coronary Artery Disease								
Spence 2014[13]	N		high	high	unclear	low	low	High
Olson 2009[14]	Y	low	unclear		unclear	unclear	low	Medium
Congestive Heart Failure								
Gattis 1999[15]	Y	low	unclear		low	low	low	Low
Murray 2007[16]	Y	low	unclear		low	unclear	low	Medium
Dyslipidemia								
Smith 2013[54]	N		high	low	unclear	low	low	Medium
Miller 2008[55]	N		high	high	unclear	unclear	low	High
Mazzolini 2005[56]	N		high	high	unclear	low	low	High
Straka 2005[57]	N		high	high	unclear	low	low	High
Ellis 2000[58]	Y	high	low		low	high	low	Medium
Bogden 1997[59]	Y	unclear	unclear		unclear	low	low	Medium
Konzem 1997[60]	N		low	high	unclear	low	high	High
Chronic Obstructive Pulmonary Disease								
Cooney 2015[20]	Y	low	low		low	unclear	low	Low
Aspinall 2012/2013[21,22]	N		unclear	high	unclear	low	low	Medium
Solomon 1998[23] **Gourley 1998**[24]	Y	low	unclear		high	unclear	low	Medium
Chronic Kidney Disease								
Pai 2009 (2 articles[18]**)**[17]	Y (pilot)	low	low		unclear	high	high	Medium
Bucaloiu 2007[19]	N		low	high	unclear	low	low	Medium

Table 2. Risk of Bias for Depression Studies

Author, Year	Randomized?	Sequence Generation	Allocation Concealment	Risk of Bias from Confounding (non-randomized)	Blinding	Incomplete Outcome Reporting	Selective Reporting	Overall
Adler 2004[25]	Y	low	low		low	high	low	Low
Capoccia 2004[26]	Y	unclear	unclear		unclear	low	low	Medium
Finley 2003[28]	Y	unclear	low		low	high	low	Medium
Finley 2002[29]	N		high	high	low	high	low	High

Table 3. Risk of Bias for Diabetes Studies

Author, Year	Randomized?	Sequence Generation	Allocation Concealment	Risk of Bias from confounding (non-randomized)	Blinding	Incomplete Outcome Reporting	Selective Reporting	Overall
McAdam-Marx 2015[53]	N		low	unclear	unclear	low	low	Medium
Rothman, 2005[39]	Y	low	low		low	low	low	Low
Skinner 2015[35]	N		low	low	unclear	low	low	Low
Chung, 2014[50]	N		high	low	unclear	low	low	Medium
Spence, 2014[13]	N		high	low	high	low	low	Medium
Brummel, 2013[46]	N		high	high	unclear	low	low	High
Ip, 2013[43]	N		unclear	low	unclear	low	low	Medium
Jacobs, 2012[38]	Y	low	low		unclear	low	low	Low
Salvo, 2012[49]	N		high	unclear	high	low	low	Medium
Cohen, 2011[32]	Y	unclear	unclear		unclear	low	low	Medium
Padiyara, 2011[45]	N		high	low	unclear	low	unclear	Medium
Pape, 2011[48]	Y	unclear	unclear		unclear	high	low	Medium
Taveira, 2011[30]	Y	low	low		unclear	low	low	Low
Heisler, 2010/2012[33,34]	Y	low	low		unclear	low	low	Low
Jameson, 2010[36]	Y	low	low		unclear	low	low	High
Johnson, 2010[42]	N		high	high	unclear	low	low	High
Taveira, 2010[31]	Y	unclear	unclear		low	low	low	Medium
Fox, 2009[47]	N		high	low	unclear	low	low	Medium
Scott, 2006[40]	Y	low	unclear		unclear	unclear	low	Medium
Kelly, 2000[44]	N		high	unclear	unclear	high	low	Medium
Odegard, 2005[51]	Y	unclear	unclear		low	high	unclear	Medium
Shane-McWhorter, 2005[41]	N		unclear	high	unclear	low	low	High

Author, Year	Randomized?	Sequence Generation	Allocation Concealment	Risk of Bias from confounding (non-randomized)	Blinding	Incomplete Outcome Reporting	Selective Reporting	Overall
Stroup, 2003[52]	Y	unclear	unclear		high	low	low	Medium
Jaber, 1996[37]	Y	unclear	unclear		high	low	low	Medium

Table 4. Risk of Bias for Hypertension Studies

Author, Year	Randomized?	Sequence Generation	Allocation Concealment	Risk of Bias from confounding (non-randomized)	Blinding	Incomplete Outcome Reporting	Selective Reporting	Overall
Carter 2015[61]	Y	unclear	unclear		unclear	low	low	Medium
Zillich 2015[66]	N		low	low	unclear	low	Low	Low
Hirsch, 2014[69]	Y	low	unclear	NA	unclear[a]	low	low	Medium
Magid 2013[70]	Y	low	unclear	NA	low	low	low	Medium
Margolis 2013[62]	Y cluster	unclear	unclear	NA	high	low	low	Medium
Magid 2011[67]	Y	low	unclear	NA	low	low	low	Medium
Carter 2009[63]	Y cluster	unclear	unclear	NA	unclear	low	low	Medium
Carter 2008[64]	Y cluster	unclear	unclear	NA	low	low	low	Medium
Green 2008[71]	Y	low	low	NA	low	low	low	Low
Hunt 2008[72]	Y	low	unclear	NA	low	high[b]	low	Medium
Borenstein 2003[73]	Y	unclear	unclear	NA	unclear	low	low	Medium
Vivian 2002[68]	Y	unclear	unclear	NA	high	low	low	Medium
Okamoto 2001[75]	Y	unclear	unclear	NA	unclear	low	low	Medium
Solomon 1998[23] Gourley 1998[24]	Y	low	unclear	NA	high	unclear	low	Medium
Erickson 1997[65]	N		high	high	unclear	high	low	High

[a] Potentially not blinded. Chart reviews were conducted by 2 clinical coordinators, one of whom was the study coordinator for this study.
[b] Very high attrition

Table 5. Risk of Bias for Polypharmacy Studies

Author, Year	Randomized?	Sequence Generation	Allocation Concealment	Risk of Bias from Confounding (non-randomized)	Blinding	Incomplete Outcome Reporting	Selective Reporting	Overall
Polypharmacy/High Risk								
Lee 2006[77]	Y (Phase 2)	low	low		high	low	low	Low
Taylor 2003[78]	Y	unclear	unclear		unclear	high	low	Medium
Malone 2000 and 2001[79,80]	Y	low	unclear		low	high	low	Medium