QUERI

Effects of Nurse-Managed Protocols in the Outpatient Management of Adults with Chronic Conditions

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PREFACE

Quality Enhancement Research Initiative's (QUERI's) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of 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.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

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

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TABLE OF CONTENTS

FIGURES

TABLES

EXECUTIVE SUMMARY

BACKGROUND

Medical management of chronic illness consumes 75 percent of every health care dollar spent in the United States, and the provision of economical, accessible, and high-quality chronic disease care is a continuing concern across health care settings. Type 2 diabetes, hypertension, hyperlipidemia, and congestive heart failure are prime examples of common chronic diseases that cause substantial morbidity and mortality and require long-term medical management and support.

For each of these disease conditions, the majority of care occurs in outpatient settings where well-established clinical practice guidelines can be used to guide treatment decisions. Despite the availability of these guidelines, practice recommendations often are not implemented which contributes to suboptimal clinical outcomes. The shortage of primary care clinicians in outpatient care settings has been identified as a barrier to the provision of comprehensive chronic disease care and provides an impetus to develop and test strategies for expanding the roles and responsibilities of other members of the interdisciplinary team to help meet the continually increasing need for chronic disease care.

In an effort to serve more Veterans and improve the quality and efficiency of chronic disease care, the Department of Veterans Affairs (VA) is implementing Patient Aligned Care Teams (PACTs)—a model of primary care transformation that builds on other widely disseminated efforts such as the chronic care model. VA PACTs are adaptations of the patient-centered medical home, which includes the following core principles: wide-ranging, team-based care; patient-centered orientation toward the whole person; care that is coordinated across all elements of the health care system and the patient's community; enhanced access to care that uses alternative methods of communication; and a systems-based approach to quality and safety. VA PACT clinical teams may include nurses (registered nurses [RNs] or licensed practical nurses [LPNs]) as well as primary care providers, clinical pharmacists, behavioral health specialists, and clinic facilitators. An organizing principle for these care teams is to utilize personnel at the highest level of their skill set. The Institute of Medicine has recommended the expansion of nurses' roles and responsibilities to allow them to practice to the full extent of their education and training.

Reports of the contributions of nurses in improving access and quality of care for patients with selected chronic conditions by using detailed structured protocols developed by or through consultation with physicians began in the late 1960s. There is now robust evidence supporting the effectiveness of nurses in providing patient education about chronic disease treatment, self-care management, and secondary prevention strategies as well as the ability of nurse practitioners (NPs) to provide effective and cost-effective primary care. As the largest segment of the health care workforce, nurses are ideally suited to collaborate with other professionals in meeting the increasing demand for chronic care. Nurses are experienced and accustomed to working in multidisciplinary teams and, with clearly defined clinical protocols and additional training, safely practice beyond their usual scope of practice and may well be able to order relevant diagnostic tests, adjust routine medication regimens, and appropriately refer complicated or unstable patients for further medical evaluation.

The VA is in the process of developing protocols and policies expanding the nurse's role as a member of PACT teams. A protocol contains a series of actions in accordance with current clinical guidelines or standards of practice that are implemented by nurses to manage a patient's condition. At the VA, there is emerging interest in allowing nurses to practice in an expanded role that includes medication initiation or titration under guidelines of protocols. The lack of certainty regarding outcomes associated with the use of clinical protocols by non-NP nurses in expanded roles led the VA to commission this evidence synthesis. We thus synthesized the current literature to describe the effects of nurse-managed protocols for the outpatient management of adults with high-impact, chronic conditions such as type 2 diabetes, hypertension, hyperlipidemia, and congestive heart failure (CHF). We examined the following key questions (KQs):

KQ 1. For adults with chronic medical conditions, do nurse-managed protocols compared with usual care improve the following outcomes?

- Nursing staff experience (e.g., satisfaction)
- Treatment adherence
- Quality measures such as
    o Biophysical markers (e.g., laboratory or physiological markers of health status such as HbA1c and blood pressure)
    o Process-of-care measures used by VA, National Quality Forum, or National Committee for Quality Assurance
- Resource utilization

KQ 2. In studies of nurse-managed protocols, how well do participating nurses adhere to the protocol?

KQ 3. Are there adverse effects associated with the use of nurse-managed protocols?

METHODS

This review was commissioned by the VA's Evidence-based Synthesis Program. We followed a standard protocol for this review; certain methods map to the PRISMA checklist. The topic was nominated after a process that included a preliminary review of published peer-reviewed literature and consultation with investigators, VA and non-VA experts, and key stakeholders (Office of Nursing Services, PACTs, and Primary Care Services).

SEARCH STRATEGY AND STUDY SELECTION

To identify relevant articles, in consultation with a master librarian, we searched MEDLINE® (via PubMed®), Cochrane Central Register of Controlled Trials, Embase®, and CINAHL® from January 1, 1980, to December 12, 2012, for peer-reviewed publications evaluating interventions that used nurse-managed protocols compared with usual care in studies targeting adults with diabetes, hypertension, hyperlipidemia, CHF, or chronic conditions. We limited the search to articles published in the English language involving human subjects 18 years of age and older.

Using prespecified inclusion and exclusion criteria, two reviewers assessed titles and abstracts for relevance to the KQs. Full-text articles identified by either reviewer as potentially relevant

were retrieved for further review and examined by two reviewers against the eligibility criteria. Disagreements on inclusion, exclusion, or the major reason for exclusion were resolved by discussion or by a third reviewer. Key eligibility criteria were randomized controlled trial or quasi-experimental study conducted in an outpatient setting; an RN or LPN used a written protocol to practice beyond their usual scope of practice that included adjustment of medications, to support the longitudinal care for patients with an eligible chronic condition (diabetes, hypertension, hyperlipidemia, or CHF); one or more outcomes of interest reported at $\geq$ 3 months.

DATA SYNTHESIS

While synthesizing relevant abstracted data, we developed a summary table describing the key outcomes and the types of study designs used to test nurse-managed protocol interventions. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis) to estimate summary effects. Where quantitative synthesis was possible (as for KQ 1), dichotomous outcomes were combined using odds ratios (ORs), and continuous outcomes were combined using mean differences (MDs) in a random-effects model. For studies with unique but conceptually similar outcomes (e.g., ordering a guideline-indicated laboratory test), we synthesized outcomes across conditions if intervention effects were sufficiently homogeneous. As a result, analyses were grouped into two major categories: (1) studies targeting cardiovascular risk factors—hyperglycemia, hypertension, hyperlipidemia and (2) studies targeting CHF.

RISK OF BIAS (QUALITY) AND STRENGTH OF EVIDENCE ASSESSMENT

For RCTs, risk of bias criteria were adequacy of randomization and allocation concealment, the comparability of groups at baseline, blinding, the completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, the validity of outcome measures, and conflict of interest. For observational studies, we addressed specific issues in the general areas of selection bias, performance bias, detection bias, and reporting bias. We assigned a summary risk of bias score (low, moderate, or high) to individual studies

In addition to rating the quality of individual studies, we evaluated the overall strength of evidence for each KQ as described in the Agency for Healthcare Research and Quality's (AHRQ's) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews." In brief, this approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains considered were impact of plausible confounders and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, low, very low, or insufficient strength of evidence was assigned after discussion by two reviewers.

PEER REVIEW

A draft version of the report was reviewed by technical experts and clinical leadership. A transcript of their comments can be found in Appendix E, which elucidates how each comment was considered in the final report.

RESULTS

Our literature search identified 2685 unique citations from a combined search of MEDLINE via PubMed, CINAHL, Embase, the Cochrane Database of Systematic Reviews, and bibliographies of key articles. After applying inclusion and exclusion criteria at both title-and-abstract and full-text review levels, the final set of articles used in this evidence report consisted of 31 articles (represented by 29 unique studies plus 2 companion articles). Of these, 18 focused on management of patients with elevated cardiovascular risk (diabetes mellitus, hypertension, or hyperlipidemia), 10 focused on management of patients with congestive heart failure (CHF), and 1 focused on resource utilization of older adults with chronic conditions. Twenty-six studies were RCTs and all compared the intervention to usual care. The overall risk of bias ratings for individual studies was: low (n=10), moderate (n=16) and high (n=3). No studies were conducted in VA settings.

All 29 studies required the nurse to have the autonomy to titrate medications; 20 of these studies allowed the nurse to independently initiate a new medication. All 29 studies used a protocol to guide the nurses, but for most studies, the protocol was limited to an algorithm describing medication titration. Only one study explicitly described the scope of practice and interactions with the team physician. All studies used an RN or equivalent as the interventionist; no studies reported the use of LPNs.

KQ 1: For adults with chronic medical conditions, do nurse-managed protocols compared with usual care improve the following outcomes?

- Nursing staff experience (e.g., satisfaction)
- Treatment adherence
- Quality measures
- Resource utilization

Key Points

- For patients with elevated cardiovascular risk, interventions using nurse-managed protocols had an overall positive effect on improving HbA1c, blood pressure, and hyperlipidemia, but effects varied substantially across studies.

- Nurse-managed protocols using an RN compared with usual care also were associated with more patients reaching target goals in total cholesterol and blood pressure.

- For patients with CHF, nurse-managed protocols using an RN were associated with lower all-cause mortality, more patients being prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocking (ACE/ARB) agent, and decreased CHF-related hospitalizations compared with usual care.

- Effects on nursing staff satisfaction were not reported.

- Effects on treatment adherence were reported infrequently but showed a pattern of improved adherence to lifestyle goals.

- The educational preparation needed to assume this expanded nurse role was not well reported.

The most robust finding is that nurse-managed protocols had a positive impact on the biophysical outcomes of chronically ill patients (Table 1). Among the studies targeting elevated cardiovascular risk, HbA1c improved by approximately 0.4 percentage points (moderate strength of evidence [SOE]); systolic and diastolic blood pressure improved by 4 mmHg and 2 mmHg, respectively (moderate SOE); total cholesterol improved by 9 mmol/l, and LDL improved by 12 mmol/l (low SOE). Among the CHF studies, nurse-managed care resulted in a significant decrease in mortality (OR 0.71; 95% CI, 0.52 to 0.96) and fewer CHF-related hospitalizations (OR 0.62; 95% CI, 0.49 to 0.80; high SOE). For both patient groups, nurse-managed protocols also were more likely to achieve target goals for markers of disease severity (e.g., lipid values) or medication-prescribing goals (moderate SOE).

Subgroup analyses showed some differences between in-person and telephone-based care studies, non-U.S. and U.S.-based studies, and among studies that incorporated self-management plans or specific behavioral interventions. Interventions delivered primarily by telephone showed significantly greater effects for total and LDL cholesterol in patients with elevated cardiovascular risk and greater mortality reductions in patients with CHF. There was a similar pattern for other outcomes but these were not statistically significant. These exploratory analyses suggest that telephone-based care may be a promising delivery mode for implementing nurse-managed protocols. Other subgroup analyses did not show any consistent pattern across outcomes.

Patient treatment adherence was reported in 6 studies, and medication adherence was reported in only 1. Effects of nurse-managed protocols on lifestyle changes and medication adherence were reported infrequently, but when reported showed an overall pattern of small positive effects (low SOE). The strength of evidence was insufficient to estimate a treatment effect for all other outcomes: nurse satisfaction, health-related quality of life, and health care costs.

Table 1. Summary of the strength of evidence for KQ 1

Outcome	Number of Studies (Patients)	Effect Estimate (95% CI)	SOE
Nurse-managed protocol intervention vs. usual care—cardiovascular risk studies			
Hemoblogin A1c	8 (2633)	MD = -0.40 (-0.63 to -0.17)	Moderate
Systolic blood pressure	12 (10,224)	MD = -3.68 (-5.67 to -1.69)	Moderate
Diastolic blood pressure	12 (10,224)	MD = -1.56 (-2.57 to -0.55)	Moderate
Blood pressure at goal	10 (9707)	OR = 1.41 (1.12 to 1.78) RD = 77 more per 1000 patients (24 to 133 more)	Moderate
Total cholesterol	9 (3494)	MD = -9.37 (-17.87 to -0.87)	Low
LDL cholesterol	6 (1119)	MD = -12.07 (-24.10 to -0.03)	Low
Cholesterol at goal	11 (9221)	OR = 1.54 (1.14 to 2.08) RD = 106 more per 1000 patients (33 to 174 more)	Moderate
Nurse-managed protocol intervention vs. usual care—congestive heart failure studies			
Mortality	10 (2836)	OR = 0.71 (0.52 to 0.96) RD = 36 fewer per 1000 patients (5 to 62 fewer)	Moderate
Total hospitalizations	6 (2352)	OR = 0.83 (0.62 to 1.10) No significant difference: RD = 32 fewer per 1000 patients (76 fewer to 18 more)	Low

Outcome	Number of Studies (Patients)	Effect Estimate (95% CI)	SOE
CHF-related hospitalizations	5 (2231)	OR = 0.62 (0.49 to 0.80) RD = 42 fewer per 1000 patients (22 to 57 fewer)	High
ACE/ARB prescribed	6 (2050)	OR = 1.15 (0.90 to 1.46) No significant difference: RD = 18 more per 1000 patients (15 fewer to 45 more)	Moderate

Abbreviations: ACE=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CHF=congestive heart failure; CI=confidence interval; LDL=low-density lipoprotein; MD=mean difference; OR=odds ratio; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; SOE=strength of evidence

KQ 2: In studies of nurse-managed protocols, how well do participating nurses adhere to the protocol?

Key Points

- Indirect evidence (e.g., improved outcomes) suggests that nurses adhere to protocols, but direct evidence (e.g., through fidelity checks) is insufficient to establish how well nurses adhere to protocols when engaged in delivering nurse-managed care.

- Only two of 29 included studies reported direct nurse adherence to treatment protocols.

Although no studies reported fidelity to important elements of the treatment protocol, indirect evidence (e.g., improved outcomes) suggests reasonable adherence to the medication elements of the protocol. Results from increased ACE/ARB treatment goals suggest nurses used the protocols. Two studies reported data on adherence to treatment protocols. When compared with usual care, nurses instituted pharmacological therapy for lipid management more often. One study reported that hypoglycemic agents and antihypertensives including ACE inhibitors, angiotensin 2 antagonists, and statins were started or doses increased by nurses following treatment protocols compared with usual care groups. However, there was no report of overall fidelity to the protocols (e.g., levels of titration, consultation with a supervisor). Thus, the data is insufficient to establish how well nurses adhere to protocols when engaged in delivering nurse-managed care.

KQ 3: Are there adverse effects associated with the use of nurse-managed protocols?

Key Points

- Adverse events were reported in only one study.

- Evidence was insufficient to establish if there are adverse effects associated with the use of nurse-managed protocols.

There was a paucity of reported adverse events in the included studies (for details on mortality, refer to section above). Adverse events include, for example, hypoglycemic or syncope episodes due to medication titration, wrong medications or dosage prescribed, drug-to-drug interactions, or increased rates of injury such as falls. Only one fair-quality U.S. study on diabetes in a health maintenance organization reported on adverse events. Severe low blood glucose events were identical (1.5%) at baseline and increased similarly, 2.9% in the control group compared with 3.1% in the intervention group (*p*=0.158). Death did not occur in either group.

RECOMMENDATIONS FOR FUTURE RESEARCH

We used the framework recommended by Robinson et al. to identify gaps in evidence and classify why these gaps exist (Table 2). This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps and classifies them as due to (1) insufficient or imprecise information, (2) biased information, (3) inconsistency or unknown consistency, and (4) not the right information. VA and other health care systems should consider their clinical and policy needs when deciding whether to invest in research to address gaps in evidence.

Table 2. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies to Consider
Patients		
Effects in patients with complex disease or multiple chronic conditions	Insufficient information	Single and multisite RCTs Quasi-experimental studies
Interventions		
Uncertainty about effects of narrowly focused (e.g., blood pressure) or multitarget (e.g., HbA1c, blood pressure, and lipids) interventions.	Insufficient information Exploratory analysis suggest possible differential effect	RCTs or quasi-experimental studies of focused versus multitarget interventions
Interventions described in sufficient detail for replication	Insufficient information	Qualitative evaluation of nurse-managed protocols to address implementation needs of stakeholders
Uncertain level of training and supervision needed	Insufficient information	Job-skills analysis Survey of authors and nurse who have evaluated nurse-managed protocols
Outcomes		
Uncertain effects on patient and staff satisfaction and experience	Insufficient information	Nonrandomized or cluster randomized, multisite implementation studies, qualitative studies
Uncertain effects on adverse events	Insufficient information	Multisite observational studies
Uncertain effects on health system costs	Insufficient information	Costs analyses, particularly in patient group with elevated CV risk
Fidelity to the intervention protocol	Insufficient information	Quantitative and qualitative approaches as part of RCT or non-RCT trials or implementation studies
Uncertain whether there would be unintended consequences to other aspects of the health care system if nurse-managed protocols were implemented	Insufficient information	Multisite observational studies

Abbreviation: HbA1c= glycosylated hemoglobin; RCT = randomized controlled trial

Our review shows that nurse-managed protocols help to improve health outcomes among patients with moderate severity of diabetes, hypertension, hyperlipidemia, and CHF. Overall, studies targeted patients with mild to moderate symptom severity. Thus, further research is needed to understand the effects of nurse-managed protocols in complex or unstable patients.

CONCLUSION

There is a pressing need to improve the medical management of adults with chronic disease, and our findings from this review of 29 studies justify testing nurse-managed protocols in the VA where detailed intervention components are monitored and data are collected. While there are many patient-level barriers that impede optimal treatment outcomes, the shortage of primary care clinicians in outpatient settings provides compelling justification to develop and test new models of chronic disease care. With the implementation of PACTs, the VA will play a critical role in reconfiguring team-based care models to expand the responsibilities of team members such as nurses to practice to the full extent of their education and training in order to improve outcomes for patients with chronic diseases.

As the largest health care workforce group, nurses are in an ideal position to collaborate with other team members in the delivery of more accessible and effective chronic disease medical care. Results from this systematic review and meta-analysis suggest that nurse-managed protocols have positive effects on the outpatient management of adults with stable, common chronic conditions such as type 2 diabetes, hypertension, hyperlipidemia, and CHF.

ABBREVIATIONS TABLE

ACE	angiotensin-converting enzyme
AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blocking
CHF	congestive heart failure
CI	confidence interval
HbA1c	glycosylated hemoglobin
KQ	key question
LDL	low-density lipoprotein
LPN	licensed practical nurse
NA	not applicable
NP	nurse practitioner
NR	not reported
OR	odds ratio
PACT	Patient Aligned Care Team
RCT	randomized controlled trial
RD	risk difference
RN	registered nurse
RR	risk ratio
SOE	strength of evidence
VA	Department of Veterans Affairs
VHA	Veterans Health Administration

EVIDENCE REPORT

INTRODUCTION

Medical management of chronic illness consumes 75 percent of every health care dollar spent in the United States,[1] and the provision of economical, accessible, and high-quality chronic disease care is a continuing concern across health care settings. Type 2 diabetes, hypertension, hyperlipidemia, and congestive heart failure are prime examples of common chronic diseases that cause substantial morbidity and mortality[2,3] and require long-term medical management and support.

For each of these disease conditions, the majority of care occurs in outpatient settings where well-established clinical practice guidelines can be used to guide treatment decisions.[4-7] Despite the availability of these guidelines, practice recommendations for standardized intervention and followup often are not implemented.[8-10] As a result, patient treatment adherence is poor or inconsistent,[11,12] often leading to suboptimal outcomes. The shortage of primary care clinicians in outpatient care settings has been identified as a barrier to the provision of comprehensive chronic disease care[13,14] and provides an impetus to develop and test strategies for expanding the roles and responsibilities of other members of the interdisciplinary team to help meet the continually increasing need for chronic disease care.

In an effort to serve more Veterans and improve the quality and efficiency of chronic disease care, the Department of Veterans Affairs (VA) is implementing Patient Aligned Care Teams (PACTs)—a model of primary care transformation that builds on other widely disseminated efforts such as the chronic care model.[15] VA PACTs are adaptations of the patient-centered medical home, which includes the following core principles: wide-ranging, team-based care; patient-centered orientation toward the whole person; care that is coordinated across all elements of the health care system and the patient's community; enhanced access to care that uses alternative methods of communication; and a systems-based approach to quality and safety. VA PACT clinical teams may include nurses (registered nurses [RNs] or licensed practical nurses [LPNs]) as well as primary care providers, clinical pharmacists, behavioral health specialists, and clinic facilitators. An organizing principle for these care teams is to utilize personnel at the highest level of their skill set. The Institute of Medicine has recommended the expansion of nurses' roles and responsibilities to allow them to practice to the full extent of their education and training.[16]

Beginning in the late 1960s, studies were conducted that assessed the contributions of nurses in improving access and quality of care for patients with selected chronic conditions by using detailed structured protocols developed by or through consultation with physicians.[17] There is now robust evidence supporting the effectiveness of nurses in providing patient education about chronic disease treatment, self-care management, and secondary prevention strategies[18-22] as well as the ability of nurse practitioners (NPs) to provide effective and cost-effective primary care.[23-26] As the largest segment of the health care workforce, nurses are ideally suited to collaborate with other professionals in meeting the increasing demand for chronic care. Nurses are experienced and accustomed to working in multidisciplinary teams and, with clearly defined clinical protocols and additional training, safely practice beyond their usual scope of practice and may well be able

to order relevant diagnostic tests, adjust routine medication regimens, and appropriately refer complicated or unstable patients for further medical evaluation.

The VA is in the process of developing protocols and policies expanding the nurse role as a member of PACT teams. A protocol contains a series of actions in accordance with current clinical guidelines or standards of practice that are implemented by nurses to manage a patient's condition.[27] At the VA, there is emerging interest in allowing nurses to practice in an expanded role that includes medication initiation or titration under guidelines of protocols.[28] The lack of certainty regarding outcomes associated with the use of clinical protocols by non-NP nurses in expanded roles led the VA to commission this evidence synthesis. We thus synthesized the current literature to describe the effects of nurse-managed protocols for the outpatient management of adults with high-impact, chronic conditions such as type 2 diabetes, hypertension, hyperlipidemia, and CHF.

METHODS

TOPIC DEVELOPMENT

This review was commissioned by the VA's Evidence-based Synthesis Program. We followed a standard protocol for this review; certain methods map to the PRISMA checklist.[29] The topic was nominated after a process that included a preliminary review of published peer-reviewed literature and consultation with investigators, VA and non-VA experts, and key stakeholders (Office of Nursing Services, PACTs, and Primary Care Services).

The Key Questions (KQs) are:

KQ 1. For adults with chronic medical conditions, do nurse-managed protocols compared with usual care improve the following outcomes?

- Nursing staff experience (e.g., satisfaction)
- Treatment adherence
- Quality measures such as
  - Biophysical markers (e.g., laboratory or physiological markers of health status such as HbA1c and blood pressure)
  - Process-of-care measures used by VA, National Quality Forum, or National Committee for Quality Assurance
- Resource utilization

KQ 2. In studies of nurse-managed protocols, how well do participating nurses adhere to the protocol?

KQ 3. Are there adverse effects associated with the use of nurse-managed protocols?

ANALYTIC FRAMEWORK

Our approach was guided by the analytic framework shown in Figure 1.

Figure 1. Analytic framework for nurse-managed protocols

Abbreviations: QOL=quality of life
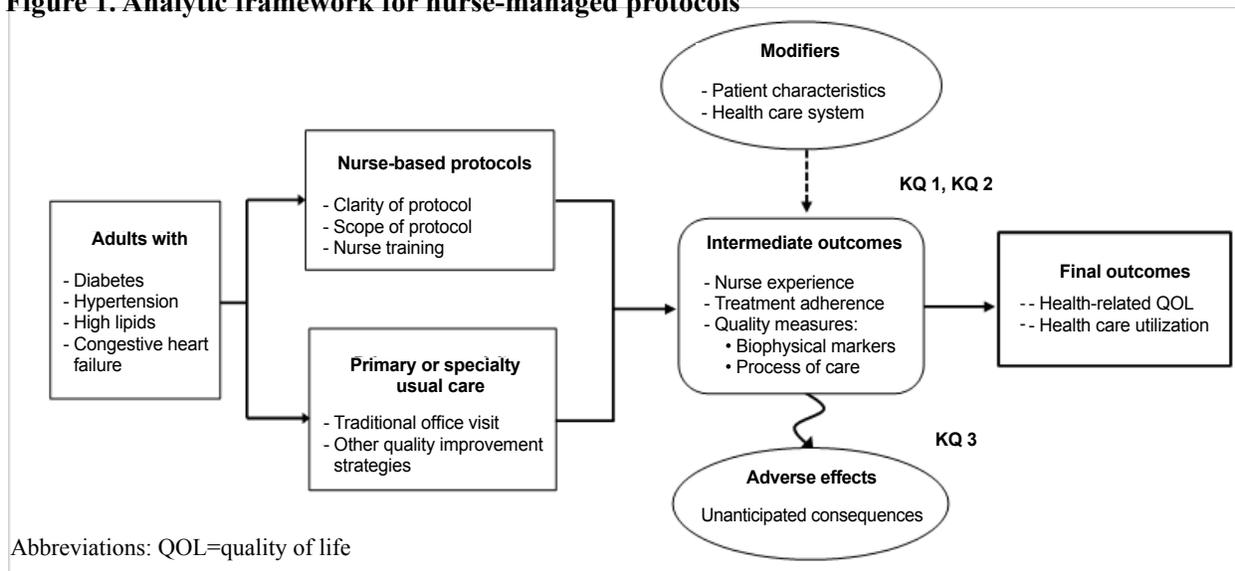
SEARCH STRATEGY

We conducted a primary review of the literature by systematically searching, reviewing, and analyzing the scientific evidence as it pertains to the KQs. To identify relevant articles, in consultation with a master librarian, we searched MEDLINE® (via PubMed®), Cochrane Central Register of Controlled Trials, Embase®, and CINAHL® from January 1, 1980, to December 12, 2012, for peer-reviewed publications evaluating interventions that used nurse-managed protocols compared with usual care in studies targeting adults with diabetes, hypertension, hyperlipidemia, CHF, or chronic conditions.

Terms such as "RN protocols" or "nurse protocols," are not yet found as key words or medical subject headings (MeSH terms) in the Library of Medicine. Therefore, we selected exemplary articles and used MeSH Analyzer (http://www.docmobi.com/mesh/) to identify high-frequency keywords supplemented with selected free-text terms used to search titles and abstracts (Appendix A). We added validated search terms for both randomized controlled trials and relevant observational studies adapted from recommendations by the Cochrane Effective Practice and Organization of Care Group. We limited the search to articles published in the English language involving human subjects 18 years of age and older. We further searched the bibliographies of exemplar studies and applicable systematic reviews for missed publications.[18,20,25,30-38] To assess for publication bias, we searched ClinicalTrials.gov to identify completed but unpublished studies meeting our eligibility criteria, an indicator of possible publication bias, but none were found as of May 30, 2013 (Appendix B).

All citations were imported into two electronic databases (for referencing, EndNote® Version X5, Thomson Reuters, Philadelphia, PA; for data abstraction, DistillerSR; Evidence Partners Inc., Manotick, ON, Canada).

STUDY SELECTION

Using prespecified inclusion and exclusion criteria, two reviewers assessed titles and abstracts for relevance to the KQs. Full-text articles identified by either reviewer as potentially relevant were retrieved for further review and examined by two reviewers against the eligibility criteria. Disagreements on inclusion, exclusion, or the major reason for exclusion were resolved by discussion or by a third reviewer. The criteria to screen articles for inclusion or exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 3.

Table 3. Summary of inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years of age) with diabetes, hypertension, hyperlipidemia, congestive heart failure, or combinations of these chronic medical conditions. In mixed samples, ≥ 80% of the sample must be selected for one of the 4 target conditions. Outpatients in a primary care setting or specialty clinic/practice. Studies with patients enrolled during a hospitalization if the majority of the intervention is delivered on an outpatient basis.	Gestational diabetes
Intervention	Intervention must involve an RN or LPN functioning beyond the usual scope of practice, which must include adjustment of medications. Activities must be based on a *written protocol* that specifies the scope of practice and is designed to support longitudinal care for chronic conditions. Interventions may be delivered by telephone or face-to-face visits.	Care plans Protocols limited to telephone triage Telecare limited to symptom or vital sign monitoring and information support Disease management protocols limited to educational interventions or assessment of treatment response
Comparator	Usual outpatient care or other quality-improvement strategy	None
Outcome	KQ 1: Study must report at least 1 of the following relevant outcomes: • Nursing staff experience using validated measures • Treatment adherence to medication or behavioral/ lifestyle recommendations • Laboratory or physiological markers of health status such as HbA1c and blood pressure (prioritizing measures associated with accepted indicators of quality of care) • Nationally recognized performance metrics related to the conditions of interest (e.g., foot exams in diabetes or proportion of patients meeting a treatment goal) • Utilization of medical resources (prioritizing hospitalizations or emergency department visits related to the condition) or health care costs (prioritizing total, inpatient and primary care outpatient costs) KQ 2: Fidelity to the nurse-managed protocol KQ 3: Adverse effects, particularly drug-related adverse effects including drug-drug interactions	No relevant outcomes
Timing	Outcomes reported ≥3 months from randomization and initiation of intervention	Outcomes reported <3 months from randomization and initiation of intervention
Setting	Outpatient setting Studies conducted in North America, Western Europe, Australia/New Zealand, and selected Caribbean countries[a]	Care model where the intervention is delivered primarily in the patient's home or community setting (e.g., community centers, workplace settings)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Study design	Study designs recommended by the Cochrane Effective Practice and Organization of Care Group: • Patient or cluster randomized controlled trials • Nonrandomized cluster controlled trials: experimental studies in which practices or clinicians are allocated to different interventions using a nonrandom method • Controlled before-and-after studies: studies in which observations are made before and after the implementation of an intervention, both in an intervention group and a control group • Interrupted time-series designs: studies that use observations at multiple time points before and after an intervention. Interrupted time series must have at least 3 measurement points prior to and after the intervention is begun.	Cross-sectional studies and other observational study designs not specifically listed as "included" study designs
Publications	English-language only Published from 1980 to present[b] Peer-reviewed, full publication	Non-English language Published before 1980 Abstract only

[a] Rationale is to include economically developed countries with sufficient similarities in health care system and culture to be applicable to U.S. medical care.
[b] Rationale is that prior to 1980, nursing education differed importantly from contemporary training; e.g., physical examination was not taught.
Abbreviations: KQ=key question; HbA1c=glycosylated hemoglobin; LPN=licensed practical nurse; RN=registered nurse

DATA ABSTRACTION

Before general use, the abstraction form templates, designed specifically for this report, were piloted on a sample of included articles and revised to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. Key characteristics abstracted include patient descriptors, setting, features of the nurse-managed protocol intervention and comparator, outcomes, and quality elements. Multiple reports from a single study were treated as a single data point. When critical data were missing or unclear, we contacted the study authors. Of 44 authors contacted, 30 responded with the requested information.

Key features relevant to applicability included the match between the sample and target populations (e.g., severity, comorbidity, age) and the training and experience of the nurse. Because many studies were conducted outside the United States, we queried authors regarding the education and scope of practice of the nurse interventionists to determine if they were closer to the U.S. equivalent of an LPN, RN, or NP (Appendix C). Selected data from published reports were then abstracted into the final abstraction form by a trained reviewer. All data abstractions were confirmed by a second reviewer. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion.

We abstracted the following key information for each included study:

- Study characteristics
  - Study design, funding source
  - Location (country and institution) and setting (clinic, etc.) of study
  - Health care system involved
  - Types of comparison groups
  - Inclusion/exclusion criteria (eligible diagnoses, etc.)
  - Number of subjects eligible for, randomized, or enrolled in and completed study

- Population characteristics
  - Sex, race, and age of sample
  - Inclusion of active duty or Veteran subjects
  - Baseline severity of symptoms or markers of conditions of interest (e.g., HbA1c)
  - Baseline performance measures

- Description of the intervention
  - Medical conditions addressed by intervention
  - Nurse's education level, special training, or certification
  - Supervision of nurse-led clinics, nurse leaders
  - Guideline or algorithm used
  - Scope of nurse's role (medication initiation and/or adjustment, etc.)
  - Other aspects of program (education, behavioral plan, self-management)
  - Mode of delivery (clinic, telephone, etc.)
  - Duration of intervention, number of planned and delivered visits

- Outcomes
  - Time points measured
  - Nursing staff satisfaction
  - Adherence (to protocol, medications, behavioral components)
  - Health-related quality of life
  - All-cause and CHF-related mortality
  - Biophysical markers (HbA1c, blood pressure, cholesterol, etc.)
  - Performance measures
  - Resource utilization (cost, hospitalizations, emergency department visits, etc.)
  - Adverse effects
  - Results from subgroup or sensitivity analyses

RISK OF BIAS (QUALITY) ASSESSMENT

We abstracted data necessary to assess the risk of bias of included studies. Across all included studies, quality criteria were applied for each study by two independent reviewers (Appendix D). Disagreements were resolved between the two reviewers or, when needed, by arbitration from a third reviewer. We used the key risk of bias criteria described in the Agency for Healthcare Research and Quality's (AHRQ's) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews"[39] adapted to this specific topic and customized to RCTs and quasi-experimental designs. For RCTs, these criteria were adequacy of randomization and allocation

concealment, the comparability of groups at baseline, blinding, the completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, the validity of outcome measures, and conflict of interest. For observational studies, we adapted AHRQ's risk of bias rating for observational studies[40] that addresses specific issues in the general areas of selection bias, performance bias, detection bias, and reporting bias. We assigned a summary risk of bias score (low, moderate, or high) to individual studies.

DATA SYNTHESIS

While synthesizing relevant abstracted data, we developed a summary table describing the key outcomes and the types of study designs used to test nurse-managed protocol interventions. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis) to estimate summary effects. Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of results reporting. For studies with unique but conceptually similar outcomes (e.g., ordering a guideline-indicated laboratory test), we synthesized outcomes across conditions if intervention effects were sufficiently homogeneous. As a result, analyses were grouped into two major categories: (1) studies targeting cardiovascular risk factors—hyperglycemia, hypertension, hyperlipidemia and (2) studies targeting CHF.

When meta-analysis was feasible, we explored the possibility of subgroup analyses to examine the consistency of effects across chronic diseases for common outcomes. Subgroup analyses involve indirect comparisons (across studies) and are subject to confounding. Thus, results were interpreted cautiously and are considered hypothesis-generating. Where quantitative synthesis was possible (as for KQ 1), dichotomous outcomes were combined using odds ratios (ORs), and continuous outcomes were combined using mean differences (MDs) in a random-effects model. To facilitate interpretation of summary ORs, we calculated the absolute risk difference using the median event rate in the control groups together with the summary ORs. For categories with multiple potential outcomes (e.g., biophysical markers) that may vary across chronic conditions, we selected a priori the outcomes to analyze for each chronic condition: HbA1c for diabetes, blood pressure for hypertension, cholesterol for hyperlipidemia, and mortality for CHF. All outcomes were transformed to common units (e.g., cholesterol values transformed to mg/dl). For meta-analyses, we used established methods[41,42] to estimate means and standard deviations (SDs) when outcomes were reported in other formats. In one instance,[43] we imputed missing SDs using estimates from similar studies. Using subgroup analyses, we explored potential sources of heterogeneity including studies conducted in the United States, the number of conditions targeted by the intervention, intervention delivery mode (telephone vs. visits), and intervention content (including self-management or behavioral strategies). We evaluated for statistical heterogeneity using Cochrane's Q and I^2 statistics. Publication bias was assessed using findings from a ClinicalTrials.gov search and funnel plots when at least 10 studies were included in the analysis (Appendix B).

Where quantitative synthesis was not feasible (as for KQs 2 and 3), we analyzed the data qualitatively. We gave more weight to the evidence from higher quality studies with more precise estimates of effect. The qualitative syntheses focused on documenting and identifying patterns in efficacy and safety of the intervention across conditions and outcome categories. We also analyzed potential reasons for inconsistency in treatment effects across studies by evaluating differences in the study population, intervention, comparator, and outcome definitions.

RATING THE STRENGTH OF EVIDENCE

In addition to rating the quality of individual studies, we evaluated the overall strength of evidence for each KQ as described in the "Methods Guide."[39] In brief, this approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains considered were impact of plausible confounders and publication bias.[44] These domains were considered qualitatively, and a summary rating of high, moderate, low, or insufficient strength of evidence was assigned after discussion by two reviewers. The five-level rating scale consists of the following definitions:

- **High** – We are very confident that the true effect lies close to that of the estimate of the effect.

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

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

- **Insufficient** – Evidence on an outcome is absent or too weak, sparse, or inconsistent to estimate an effect.

When a rating of high, moderate, low, or very low was not possible or was imprudent to make, a rating of insufficient was assigned.

PEER REVIEW

A draft version of the report was reviewed by technical experts and clinical leadership. A transcript of their comments can be found in Appendix E, which elucidates how each comment was considered in the final report.

RESULTS

LITERATURE SEARCH

The flow of articles through the literature search and screening process is illustrated in Figure 2. Our search identified 2650 unique citations from a combined search of MEDLINE via PubMed (n=1844), CINAHL (n=388), Embase (n=360), and the Cochrane Central Database (n=58). Manual searching of included study bibliographies and review articles added 35 more citations. Another article missed in our search[28] was identified by a reviewer, for a total of 2686 unique citations. After applying inclusion and exclusion criteria at the title-and-abstract level, 340 full-text articles were retrieved and screened. Of these, 309 were excluded at the full-text screening stage, leaving 31 articles (represented by 29 unique studies plus 2 companion articles) for data abstraction. Note that four studies were excluded because we could not verify whether nurses had the authority to initiate or titrate medications and there was no response to our author query for clarification.[45-48] Of the 29 unique studies, 26 are RCTs and 3 are non-RCTs.

Figure 2. Literature flow diagram

Search results = 2686 references → Excluded = 2346 references: Excluded at title/abstract level

Retrieved for full-text review = 340 references → Excluded = 309 references
- Not English, Westernized country, or full publication = 55
- Not adults with disease of interest, or conducted in an outpatient medical setting = 19
- Not an eligible study design or comparator is not usual care or quality-improvement strategy = 76
- Not intervention of interest = 153
- Not outcome of interest = 6

Included 29 unique studies + 2 companion articles[a]

[a] Refer to Glossary for a definition of companion articles.

DESCRIPTION OF INCLUDED STUDIES

We identified 29 studies that met our inclusion criteria.[43,49-76] Of these, 18 focused on management of patients with elevated cardiovascular risk (diabetes mellitus, hypertension, or hyperlipidemia),[43,49,51-53,56,57,60,62,63,65,67-72,76] 10 focused on management of patients with congestive heart failure (CHF),[50,54,55,59,61,64,66,73-75] and 1 focused on resource utilization of older adults with chronic conditions.[58] Detailed study characteristics for each of the 29 studies are in Appendix F.

Twenty-six studies were RCTs; among the remaining three, two were controlled before-and-after

studies[67,71] and one was a nonrandomized controlled clinical trial.[58] Of these, two focused on diabetes and one on older adults. The comparator was usual care in all but one study, which used a reverse-control design where each intervention served as the control for the other. Eighteen of these studies were conducted in Western Europe and 11 in the United States; none were reported to be conducted in military or VA settings.

All 29 studies required the nurse to have the autonomy to titrate medications; however, only 20 reported that the nurse was allowed to independently initiate a new medication. All 29 studies used a protocol to guide the nurses, but only 23 provided the actual algorithm or a citation to it; 6 studies did not.[50,57,58,64,66,72] For most studies, the protocol was limited to an algorithm describing medication titration. Only one study explicitly described the scope of practice and interactions with the team physician. All studies used an RN or equivalent as the interventionist; no studies reported the use of LPNs. For studies conducted outside the United States, authors who were queried about the type of nurse used indicated that they most closely resembled the U.S. equivalent of an RN. Next, we give further details and analysis of the included studies organized by KQ.

KEY QUESTION 1. For adults with chronic medical conditions, do nurse-managed protocols compared with usual care improve the following outcomes?
- **Nursing staff satisfaction**
- **Treatment adherence**
- **Quality measures**
- **Resource utilization**

Key Points
- For patients with elevated cardiovascular risk, nurse-managed protocols:
  - Had an overall positive effect on improving HbA1c, blood pressure, and hyperlipidemia, but intervention effects varied substantially across studies.
  - Were associated with more patients reaching target goals in total cholesterol and blood pressure compared with usual care.

- For patients with CHF, nurse-managed protocols were associated with:
  - Lower all-cause mortality
  - More patients being prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocking (ACE/ARB) agent
  - Decreased CHF-related hospitalizations compared with usual care

- Effects on nursing staff satisfaction were not reported.

- Effects on treatment adherence were reported infrequently but showed a pattern of improved adherence to lifestyle goals.

- The educational preparation needed to assume this expanded nurse role was not well reported.

Studies Targeting Elevated Cardiovascular Risk: Diabetes, Hypertension, Hyperlipidemia

Eighteen studies targeted patients with elevated cardiovascular risk.[43,49,51-53,56,57,60,62,63,65,67-72,76] Table 4 summarizes the study and patient characteristics. A nurse-led clinic was used to deliver the interventions in 14 of these studies.[49,51-53,57,62,63,65,67-71,76] Supervision of the nurse was almost exclusively by a physician, and half the studies reported this as specifically a primary care physician. All nurse interventionists were RNs or equivalent and did not meet the threshold of advanced practice nursing. Of the studies that reported the nurses' training, 3 studies used specialists (e.g., diabetes-certified), 10 reported study-specific training, and 1 used nurse case managers.

Additional intervention was delivered by the nurse in 16 of the 18 studies and included education, behavioral (i.e., motivational interviewing), or self-management. In 12 studies, the intervention was exclusively clinic-delivered, and in 4 studies either exclusively telephone-delivered or a combination of telephone- and clinic-delivered. The other two studies did not report additional intervention beyond medication titration.[52,63] Outcomes were assessed at 6 to 36 months, with most studies reporting outcomes at 12 months or longer.

Overall, baseline characteristics showed that patients with diabetes had elevated HbA1c of approximately 8.0 percent or more, most patients with hypertension had stage 1 or moderate hypertension, and patients with hyperlipidemia had borderline high to near ideal lipid levels.

We assessed the risk of bias for each study and found that 2 studies had high risk of bias,[57,71] 12 had moderate risk,[43,49,51,52,56,63,65,67-70,76] and 4 had low risk.[53,60,62,72] A rating of moderate risk was largely due to possible contamination from a concurrent intervention, outcome assessors not blinded, or incomplete outcome data. In the study with high risk of bias, there was inadequate randomization. Overall, there was moderate risk of bias in these studies.

Table 4. Study and patient characteristics of included diabetes, hypertension, and hyperlipidemia studies[a]

Study Characteristics	Cardiovascular Risk Studies
N studies (N patients)	18 studies (23,004 patients)[b]
Study design: N studies (%) 　RCT 　Non-RCT	 16 (89%) 2 (11%)
Setting: N studies (%) 　General medical 　Medical specialty 　Primary clinic and specialty 　Telephone- and clinic-delivered care	 12 (67%) 3 (17%) 2 (11%) 1 (5.5%)
Intervention target: N studies (%) 　Glucose 　Blood pressure 　Lipids	 12 (67%) 15 (83%) 14 (78%)

Study Characteristics	Cardiovascular Risk Studies
Intervention delivery: N studies (%)	
Clinic visits	15 (83%)
Primarily telephone	3 (17%)
Balance of visits and telephone	–
Nurse training: N studies (%)	
Specialist (i.e., clinical certification or diabetes nurse educator)	3 (17%)
Received study-specific training	10 (55%)
Case manager	1 (5.5%)
Not described	4 (22%)
Medication initiation: N studies (%)	12 (67%)
Education or behavioral strategies: N studies (%)	
Education	16 (89%)
Specific behavioral strategy (e.g., motivational interviewing)	3 (17%)
Self-management plan	9 (50%)
Risk of bias: N studies (%)	
Low	4 (22%)
Moderate	12 (67%)
High	2 (11%)
Patient characteristics	
Age: median (range)	58.3 (34.7 to 72.1)[c]
Sex: N patients (%)[d]	
Female	4126 (47%)
Male	4716 (53%)
Race: N patients (%)	
Black	52 (0.2%)
Hispanic	653 (2.8%)
White	2280 (9.9%)
Other	636 (2.8%)
Not reported	19,383 (84.3%)[e]
Disease severity: median (range)	
HbA1c (%)	8.1 (8.0 to 8.2), NR=16
SBP (mm Hg)	149.4 (119 to 161.3), NR=4
DBP (mm Hg)	80 (69 to 87.7), NR=4
LDL (mg/dl)	124.9 (85.3 to 131.5), NR=10

[a] Excluded from this table is one study[58] conducted in older adults with complex conditions that included diabetes, hypertension, and congestive heart failure.

[b] Number of participants represents the grand mean of 22,839 and 23,170 because one included study[68] randomized such that hypertension and hyperlipidemia results were reported on two different but overlapping populations.

[c] Age represents 16 of the 18 studies because two studies[53,68] did not report age or reported it as a categorical variable.

[d] Sex represents 17 of the 18 studies because one study[68] did not report the sex distribution of their populations.

[e] Race represents the grand mean of 19,218 and 19,549 because one study[68] reported on an overlapping sample.

Abbreviations: DBP=diastolic blood pressure; HbA1c=glycosylated hemoglobin; LDL=low-density lipoprotein; SBP=systolic blood pressure

Nursing Staff Satisfaction

None of the included studies reported on nursing staff satisfaction.

Treatment Adherence

Treatment adherence was reported in five studies, of which four were RCTs. Behavior adherence was reported in four adherence was reported in four,[49,56,65,67] and medication adherence was

reported in one.[72] Reported outcomes on behavioral adherence varied. Three studies reported effects on smoking, two of those showing small, nonstatistically significant decreases in the intervention groups (risk difference <2%),[65,67] and one showing a 9-percent reduction in smoking compared with the control group (p=.05).[49]

Effects on physical activity were reported in three studies,[49,56,67] all showing increased physical activity or exercise capacity. Meulepas et al.,[67] found a MD of 0.4 improvement on a 5-point Likert scale (95% CI, 0.03 to 0.8). Allison et al.,[49] reported an increase in minutes of exercise per week (183 ± 118) compared with control (127 ± 107, p<0.01) and Debusk et al.[56] reported increased functional capacity measured at 6 months (MD 9.3; 95% CI, 9.0 to 9.6) compared with usual care (MD 8.4; 95% CI, 8.1 to 8.7). Allison et al.[49] reported no significant differences between the intervention and control on diet, but weight (kilograms) decreased more in the intervention group (-0.3 ± 4.9) compared with control (+1.7 ± 5.0, p=0.03). Debusk et al.[56] found that among the intervention group the proportion of participants consuming a diet very low in cholesterol and saturated fat increased from 31 percent at baseline to 88 percent at 90 days (p<0.001).

Among the study that reported treatment adherence to medication, Rudd, et al.[72] reported higher medication adherence in the intervention group compared with control (p=0.03). The intervention groups' rate of daily adherence during the 6-month study period was 80.5 percent ± 23.0 percent, versus 69.2 percent ± 31.1 percent in the usual care group. In summary, effects of nurse-managed protocols on indicated lifestyle changes and medication adherence were reported infrequently, but when reported show an overall pattern of small positive effects.

Quality Measures
Biophysical Markers

Hemoglobin A1c (HbA1c). Of the 15 studies conducted in patients with diabetes, 10 studies involving 2633 patients targeted glucose control. Figure 3 shows the forest plot of the random-effects meta-analysis of nurse-managed protocols on hemoglobin A1c (HbA1c) stratified by RCT versus non-RCT. Nurse-managed protocols were associated with lower HbA1c compared with usual care in the RCTs (MD -0.40; 95% CI, -0.63 to -0.17) with effects varying significantly (Q=23.19, degrees of freedom [df]=7, p=0.002; I^2=70%).

We performed subgroup analyses comparing studies conducted in the United States versus other countries, studies targeting HbA1c alone versus multiple conditions, studies incorporating self-management plans or specific behavioral interventions versus those that did not, and studies delivering the intervention primarily by clinic visits versus telephone interventions. These analyses showed greater effects for studies conducted in the United States (-0.92 vs. -0.23, p=0.0003) and for studies targeting only HbA1c (-1.1 vs. -0.31, p=0.005); treatment variability was reduced in these subgroups. No studies that targeted glucose control used telephone-based care. Thus, nurse-managed protocols were associated with a mean decrease in HbA1c, but effects varied markedly. Exploratory subgroup analysis suggests some of the variability in intervention effects may be explained by country and by the specificity of the intervention (Appendix G).

Effects of nurse-managed protocols on HbA1c from the non-RCTs were in the same direction (MD -1.12; 95% CI, -2.99 to 0.74) yet with higher variability and effects varying widely (Q=33.86, df=1, p<0.001; I^2=97%). Both non-RCTs[67,71] found statistically significant reductions in HbA1c from baseline to followup among patients participating in a nurse-managed protocol.

Figure 3. Effects of nurse-managed protocols on hemoglobin A1c
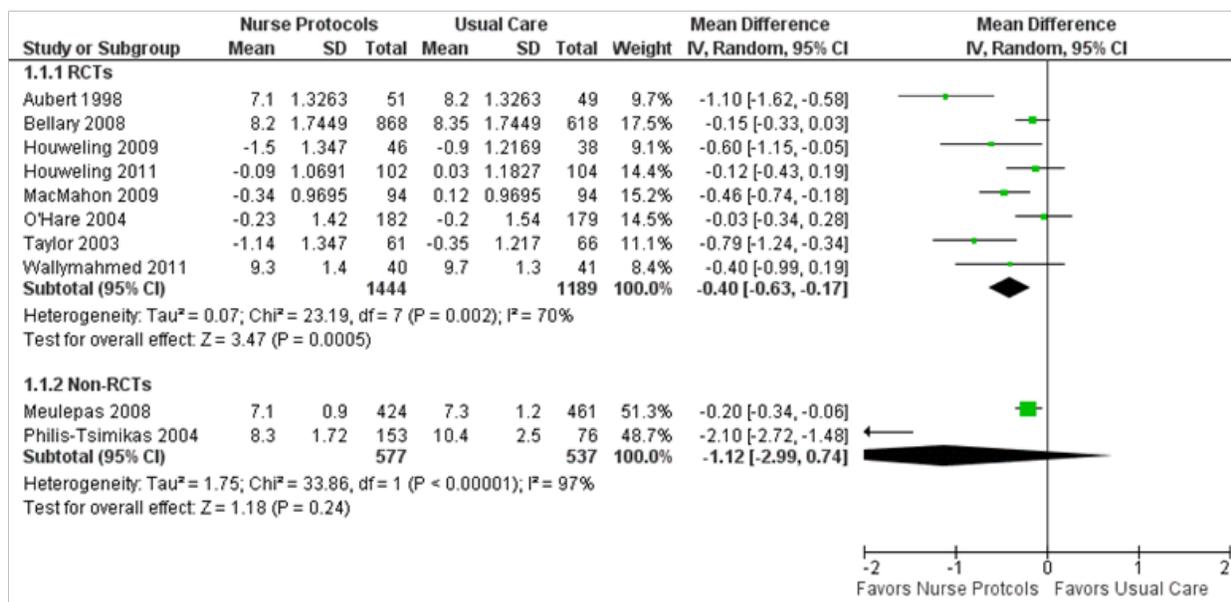
Abbreviations: CI=confidence interval; RCT=randomized controlled trial; SD=standard deviation

Systolic and diastolic blood pressure (SBP, DBP). Of the 18 studies conducted in patients with elevated cardiovascular risk, 14 targeted blood pressure control. Twelve RCTs (10,224 patients) and one non-RCT (885 patients) were included in the quantitative analyses. Compared with usual care, nurse-managed protocols were associated with lower SBP (Figure 4) and DBP (Figure 5).

In analyses restricted to RCTs, the intervention was associated with lower SBP (MD -3.68; 95% CI, -5.67 to -1.69) and DBP (MD -1.56; 95% CI, -2.57 to 0.55). For both outcomes, intervention effects varied significantly. Because of variability in effects between studies, we conducted a sensitivity analysis to evaluate this variability. We excluded the studies by Bebb et al.[52] and New et al.,[68] which involved training nurses to implement nurse-managed protocols but not in directly delivering the intervention. Without these studies, intervention effects were only slightly stronger (SBP MD 5.1; 95% CI, -7.70 to -2.51; DBP MD -1.64; 95% CI, -2.76 to -0.52), but variability in intervention effects remained high ($I^2 \geq 67\%$). Funnel plots, interpreted visually, suggest possible publication bias when examining effects on SBP but not for DBP (Appendix B).

Effects of nurse-managed protocols on SBP and DBP from the one non-RCT[67] were in the same direction, with nonstatistically significant reductions in SBP from baseline to followup among patients participating in a nurse-managed protocol. Due to only one non-RCT, a test of heterogeneity was not possible. Thus overall, nurse-managed protocols were associated with a mean decrease in SBP and DBP.

We performed subgroup analyses to explore for differences in intervention effects between studies conducted in the United States versus other countries, studies targeting BP alone versus multiple conditions, studies incorporating self-management plans or specific behavioral interventions versus those that did not, and studies delivering the intervention primarily by clinic visits versus telephone interventions. There were no statistically significant differences in treatment effects for any of these subgroup analyses (Appendix G).

Figure 4. Effects of nurse-managed protocols on SBP

Abbreviations: CI=confidence interval; RCT=randomized controlled trial; SD=standard deviation

Figure 5. Effects of nurse-managed protocols on DBP
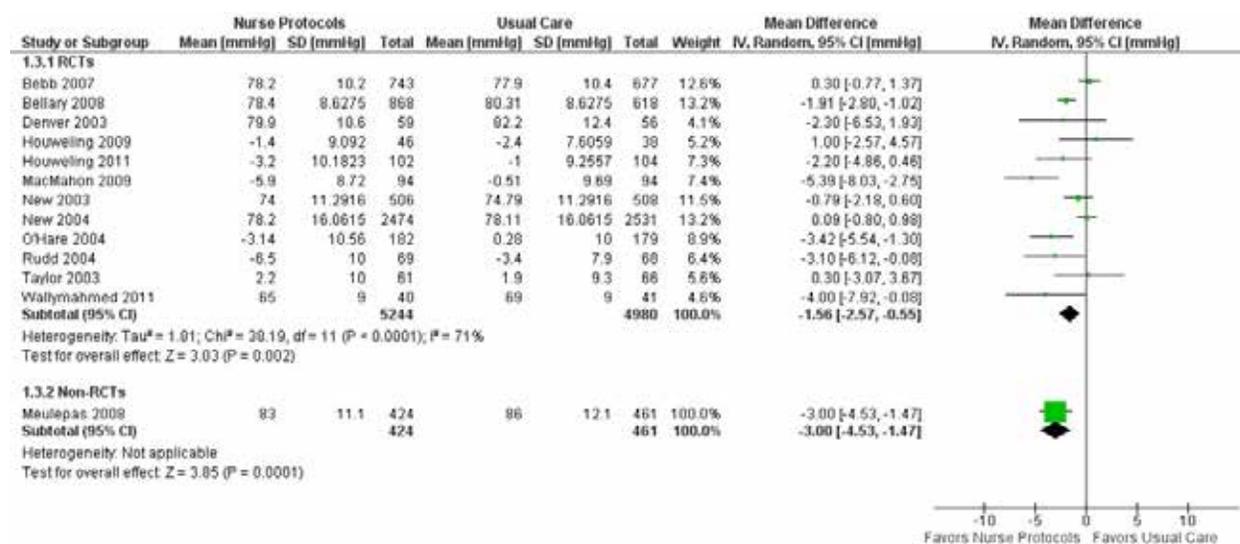
Abbreviations: CI=confidence interval; RCT=randomized controlled trial; SD=standard deviation

Total cholesterol and low-density lipoprotein (LDL) cholesterol. Of the 18 studies conducted in patients with elevated cardiovascular risk, 14 targeted hyperlipidemia. Nine RCTs (3494 patients) and two non-RCTs (1114 patients) were included in the quantitative analyses. Compared with usual care, nurse-managed protocols were associated with lower total cholesterol (Figure 6) and lower LDL cholesterol (Figure 7). Overall, fewer studies reported LDL than total cholesterol.

In analyses restricted to RCTs, the intervention was associated with lower total cholesterol (MD -9.37; 95% CI, -17.87 to 0.87) and LDL cholesterol (MD -12.07; 95% CI, -24.10 to -0.03) with marked variability in intervention effects ($I^2 \geq 89\%$). We conducted subgroup analyses comparing studies conducted in the United States versus other countries, studies targeting hyperlipidemia alone versus multiple conditions, studies incorporating self-management plans or

specific behavioral interventions versus those that did not, and studies delivering the intervention primarily by clinic visits versus telephone interventions. These analyses showed greater effects for studies that were telephone-based compared with in-person care in total cholesterol (-24.33 vs. -7.17, *p*=0.0008) and LDL cholesterol (-24.7 vs. -9.22, *p*=0.03). Treatment variability was reduced in these subgroups. Exploratory subgroup analysis suggests some of the variability in intervention effects may be explained by mode of delivery (Appendix G).

Effects of nurse-managed protocols on total cholesterol and LDL cholesterol from the two non-RCTs[67,71] were in the same direction, with nonstatistically significant reductions in total cholesterol. However, there was a statistically significant reduction (MD -25.90; 95% CI, -42.41 to -9.39) in LDL cholesterol in one non-RCT[71] from baseline to followup among patients participating in a nurse-managed protocol. Due to only one non-RCT assessing LDL cholesterol, a test of heterogeneity was not possible. Thus overall, nurse-managed protocols were associated with a mean decrease in total cholesterol and LDL cholesterol.

Figure 6. Effects of nurse-managed protocols on total cholesterol
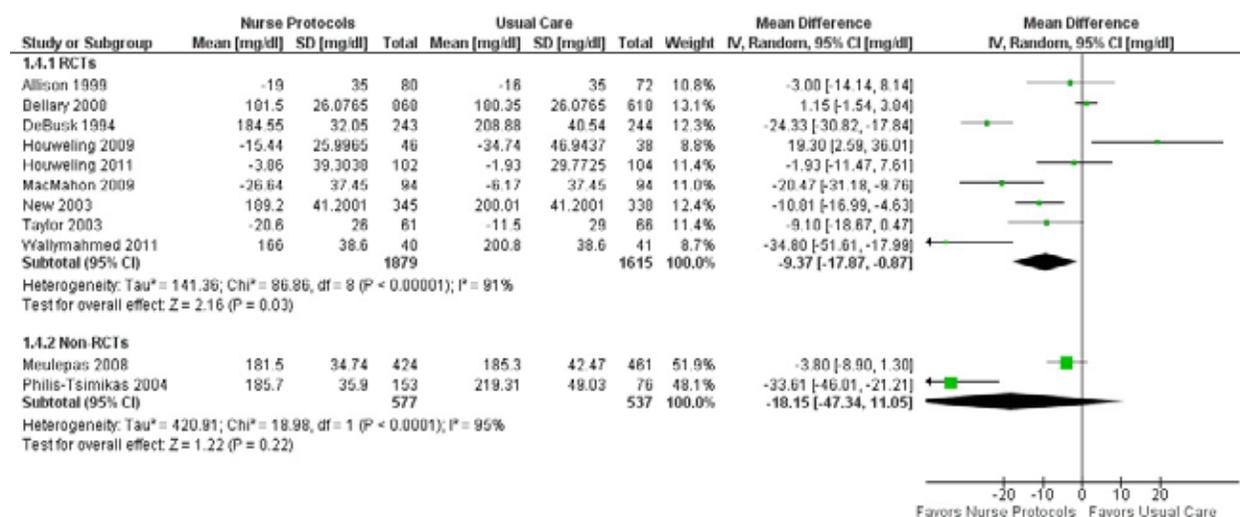
Abbreviations: CI=confidence interval; RCT=randomized controlled trial; SD=standard deviation

Figure 7. Effects of nurse-managed protocols on LDL cholesterol
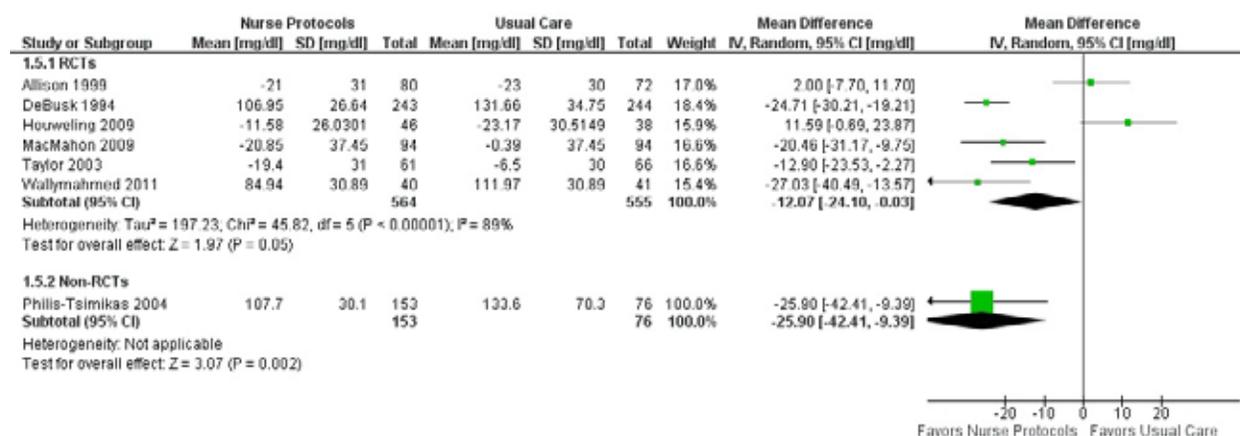
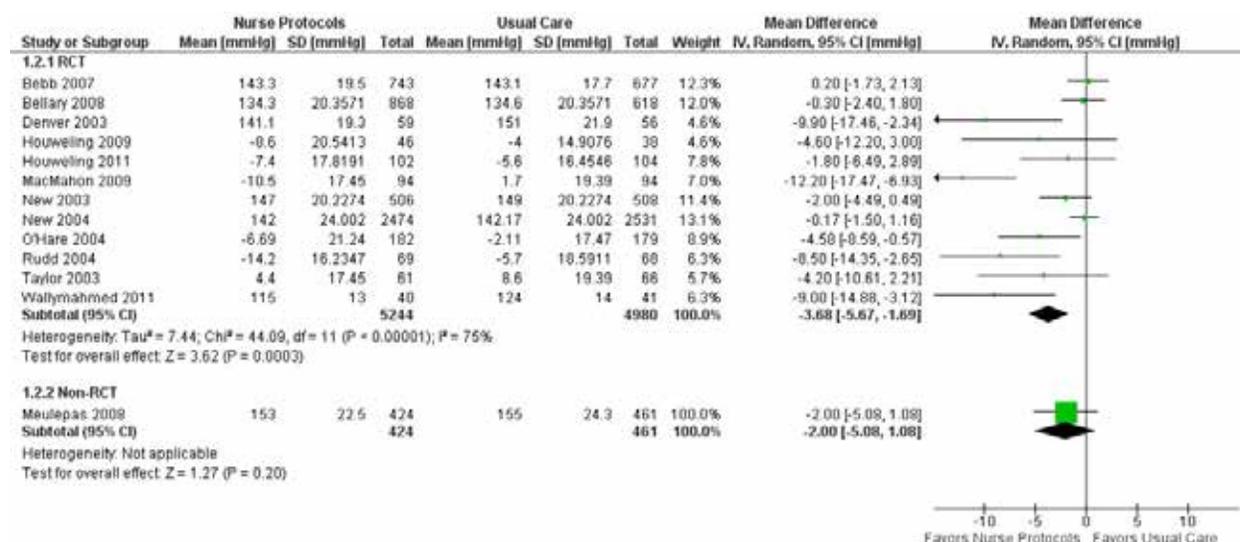Abbreviations: CI=confidence interval; RCT=randomized controlled trial; SD=standard deviation

Process-of-care measures

Target blood pressure values. Of the 18 studies conducted in patients with elevated cardiovascular risk, 11 focused on achieving target blood pressure values. Figure 8 shows the forest plot of the random-effects meta-analysis of nurse-managed protocols on the process measure of achieving target total cholesterol values stratified by RCT and non-RCT. Ten RCTs (9707 patients) and 1 non-RCT (885 patients) were included in the quantitative analysis. Some studies did not report this performance metric but did report change in blood pressure.[70-72] One study reported effects on SBP and DBP but, as a diabetes-focused study, had no expectations of effects on blood pressure.[51] These were excluded from this analysis. It is important to note that target blood pressure goals may have varied by study.

Nurse-managed protocols were significantly more likely to achieve target blood pressure values compared with controls (OR 1.41; 95% CI, 1.12 to 1.78), with high variability in treatment effects (Q=35.20, df=9, p<0.001; I^2=74%). Because of variability in effects between studies, we conducted a sensitivity analysis to evaluate this variability. We excluded two studies[52,68] that trained practices to implement nurse-managed protocols rather than delivering the intervention directly. Without this study, effects were slightly larger (OR 1.69; 95% CI, 1.18 to 2.43), and variability in treatment effects remained high (I^2=72%). We performed subgroup analyses to explore for differences in intervention effects between studies conducted in the United States versus other countries, studies assessing target blood pressure values alone versus multiple process-of-care measures, studies incorporating self-management plans or specific behavioral interventions versus those that did not, and studies delivering the intervention primarily by clinic visits versus telephone interventions. There were no telephone-based studies and no statistically significant differences in treatment effects for any of the other subgroup analyses (Appendix G).

Using the summary odds ratio (OR) and median event rate from the control arm of the trials, though not statistically significant, we estimated the absolute treatment effect as a risk difference of 77 more achieved target total blood pressure values per 1000 patients (95% CI, 24 to 133 more). Funnel plots suggested some asymmetry but likely no clear indication of publication bias (Appendix B).

In the one non-RCT,[67] nurse-managed protocols were associated with a nonstatistically significant increase on achieving target blood pressure values (OR 1.08; 95% CI, 0.83 to -1.41).

Figure 8. Effects of nurse-managed protocols on achieving target blood pressure values

Study or Subgroup	Nurse Protocols Events	Total	Usual Care Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.7.1 RCTs						
Bebb 2007	245	743	202	677	16.1%	1.16 [0.92, 1.45]
Bellary 2008	310	868	191	618	16.2%	1.24 [1.00, 1.55]
Denver 2003	20	53	6	50	4.1%	4.44 [1.61, 12.30]
Houweling 2009	12	46	9	38	4.2%	1.14 [0.42, 3.08]
Houweling 2011	26	102	22	104	7.7%	1.28 [0.67, 2.44]
MacMahon 2009	67	94	30	92	8.0%	5.13 [2.75, 9.57]
New 2003	135	506	122	506	14.8%	1.15 [0.86, 1.52]
New 2004	1192	2474	1212	2531	18.2%	1.01 [0.91, 1.13]
Taylor 2003	32	61	28	66	7.0%	1.50 [0.74, 3.02]
Wallymahmed 2011	32	39	29	39	3.7%	1.58 [0.53, 4.68]
Subtotal (95% CI)		**4986**		**4721**	**100.0%**	**1.41 [1.12, 1.78]**
Total events	2071		1851			

Heterogeneity: Tau² = 0.07; Chi² = 35.20, df = 9 (P < 0.0001); I² = 74%
Test for overall effect: Z = 2.88 (P = 0.004)

Study or Subgroup	Nurse Protocols Events	Total	Usual Care Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.7.2 Non-RCTs						
Meulepas 2008	190	424	198	461	100.0%	1.08 [0.83, 1.41]
Subtotal (95% CI)		**424**		**461**	**100.0%**	**1.08 [0.83, 1.41]**
Total events	190		198			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favors Usual Care   Favors Nurse Protocols

Abbreviations: CI=confidence interval; RCT=randomized controlled trial

Target total cholesterol values. Of the 18 studies conducted in patients with elevated cardiovascular risk, 11 targeted total cholesterol target values. Figure 9 shows the forest plot of the random-effects meta-analysis of nurse-managed protocols on the process measure of achieving target total cholesterol values. Eleven RCTs with 9221 patients were included in the quantitative analysis. Nurse-managed protocols were significantly more likely to achieve target total cholesterol values compared with controls (OR 1.54; 95% CI, 1.14 to 2.08), with moderate variability in treatment effects (Q=71.59, df=10, p<0.001; I^2=56%). Because of variability in effects between studies, we conducted a sensitivity analysis to evaluate this variability. We excluded one study,[68] which trained nurses to implement nurse-managed protocols, rather than delivering the intervention directly. Without this study, effects were slightly larger (OR 1.64; 95% CI, 1.11 to 2.41).

Using the summary OR and median event rate from the control arm of the RCTs, we estimated the absolute treatment effect as a risk difference of 106 more achieved target total cholesterol values per 1000 patients (95% CI, 33 to 174 more). It is important to note that target cholesterol goals may have varied by study. Funnel plots did not suggest publication bias (Appendix B).

We performed subgroup analyses to explore for differences in intervention effects between studies conducted in the United States versus other countries, studies assessing target total cholesterol values alone versus multiple process-of-care measures, studies incorporating self-management plans or specific behavioral interventions versus those that did not, and studies delivering the intervention primarily by clinic visits versus telephone interventions. There were no statistically significant differences in treatment effects for any of these subgroup analyses (Appendix G).

Figure 9. Effects of nurse-managed protocols on achieving target total cholesterol values

Study or Subgroup	Nurse Protocols Events	Total	Usual Care Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.6.1 RCTs						
Allison 1999	41	80	36	72	8.4%	1.05 [0.56, 1.99]
Bellary 2008	411	867	311	617	12.6%	0.89 [0.72, 1.09]
DeBusk 1994	103	243	37	244	10.5%	4.12 [2.67, 6.34]
Fischer 2012	228	381	178	381	12.0%	1.70 [1.28, 2.26]
Houweling 2009	42	46	35	38	2.9%	0.90 [0.19, 4.29]
Houweling 2011	81	102	88	104	7.6%	0.70 [0.34, 1.44]
MacMahon 2009	79	94	58	94	7.9%	3.27 [1.64, 6.52]
New 2003	180	345	139	338	11.8%	1.56 [1.15, 2.11]
New 2004	1386	2495	1351	2475	13.2%	1.04 [0.93, 1.16]
Taylor 2003	28	61	25	66	7.7%	1.39 [0.69, 2.82]
Wallymahmed 2011	31	39	18	39	5.4%	4.52 [1.66, 12.29]
Subtotal (95% CI)		4753		4468	100.0%	1.54 [1.14, 2.08]
Total events	2610		2276			

Heterogeneity: Tau² = 0.18; Chi² = 71.59, df = 10 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.79 (P = 0.005)

Abbreviations: CI=confidence interval; RCT=randomized controlled trial; SD=standard deviation

Other performance measures. Other performance measures of interest were rarely reported. Achieving target urine microalbumin-to-creatinine ratio was reported to reach 100 percent in nurse-managed protocols in one controlled before and after study.[71] The same study reported 100 percent of patients achieved foot exam goals and 81 percent of patients achieved eye exam goals, and a second study using a similar design by Meulepas and colleagues[67] reported a nonsignificant increase in intervention patients achieving the outcome goals of eye exams (*p*=0.1) and foot exams (*p*=0.2) compared with control. Reduction in the proportion of patients with very poor glycemic control (A1c ≥8.5) was achieved in half the patients in one study (OR 1.69; 95% CI, 1.25 to 2.29).[67]

Resource Utilization

Total costs

Reporting of resource utilization was limited and noted in only three studies.[60,63,69] Houweling et al.[63] reported total salary costs to be significantly lower in the intervention group (€114.6 ± 50.4) compared with the standard of care (€138.3 ± 48.3; *p*<0.001). In this same study, total costs for medication were reported to be lower, though not statistically significant, in the intervention groups (€136.3 ± 91.9) compared with control (€149.0 ± 94.4; *p*=NS) at study completion.

Inpatient costs were reported to be significantly lower in two other studies. One described total inpatient costs for the intervention group at $869,535 versus $1,702,682 for the control (*p*=0.02).[60] The other reported decreases in costs by sex, with the intervention groups achieving a decrease of $606 for men and $888 for women with hypertension.[69] Further, outpatient costs were reported to be lower, albeit nonsignificant, with total costs reported at $1,237,270 in the nurse-managed protocol group versus $1,381,900 in the control group (*p*=0.47).[69]

Studies Targeting Congestive Heart Failure

Ten randomized trials evaluated nurse-managed protocols in 2836 patients with
CHF.[50,54,55,59,61,64,66,73-75] Table 5 summarizes the study and patient characteristics. A nurse-led clinic
delivered the interventions in 5 studies.[59,64,66,74,75] Supervision of the nurse was almost exclusively
by a physician, usually a primary care physician, and in some instances, a cardiologist. Outcomes
were assessed at 6 to 18 months, with most reporting outcomes at 12 months or later. All nurse
interventionists were RNs or equivalent and did not meet the threshold of advanced practice
nursing. Of the studies that reported the nurses' training, three used specialists (i.e., cardiac-
certified), three reported study-specific training, and one used nurse case managers.

In nine studies, additional intervention was delivered by the nurse and included education,
behavioral (i.e., motivational interviewing), or self-management. In six studies, the intervention
was exclusively clinic-delivered, and in four studies either exclusively telephone-delivered or a
combination of telephone- and clinic-delivered.

Overall, baseline characteristics demonstrate that most studies targeting patients with CHF
had on average stage III (moderate) heart failure according to the New York Heart Association
functional class. Measurement of left ventricular ejection fracture (LVEF) assessed during
hospitalization of patients was not a focus of these studies and was not reliably reported.

We assessed risk of bias for each study and found that five studies had moderate risk of
bias,[54,59,64,66,74] and five had low risk.[50,55,61,73,75] A rating of moderate risk was largely due to
possible contamination from a concurrent intervention, unclear risk of protocol variation, or
outcome assessors not blinded. Overall, there was low to moderate risk of bias in these studies.

Table 5. Study and patient characteristics of included CHF studies[a]

Study Characteristics	Congestive Heart Failure Studies
N studies (N patients)	10 (2836)

Study design: N studies (%)
  RCT
  Non-RCT
	
	10 (100%)
	–

Setting: N studies (%)
  General medical
  Medical specialty
  Telephone- and clinic-delivered care
  Not reported/unclear
	
	–
	3 (30%)
	6 (60%)
	1 (10%)

Intervention delivery: N studies
  Clinic visits
  Primarily telephone
  Balance of visits and telephone
	
	4
	5
	1

Nurse training: N studies (%)
  Specialist (i.e., clinical certification or diabetes nurse educator)
  Received study-specific training
  Case manager
  Not described
	
	4 (40%)
	5 (50%)
	–
	1 (10%)

Medication initiation: N studies (%)	8 (80%)

Educational or behavioral strategies: N studies (%)
  Education
  Specific behavioral strategy (e.g., motivational interviewing)
  Self-management plan
	
	9 (90%)
	3 (30%)
	5 (50%)

Study Characteristics	Congestive Heart Failure Studies
Risk of bias: N studies (%)	
Low	6 (60%)
Moderate	4 (40%)
High	–
Patient characteristics	
Age: median (range)	72 (53 to 80)
Sex N patients (%)	
Female	988 (35%)
Male	1870 (65%)
Race: N patients (%)	
Black	988 (35%)
Hispanic	1870 (65%)
White	–
Other	–
Not reported	–
Disease severity: median (range)	
NYHA, class I-II (%)	50 (40.9 to 62)
NYHA, class III-IV (%)	50 (38 to 59)
Not reported	7 studies

[a] Excluded from this table is one study conducted in older adults with complex conditions that included diabetes, hypertension, and congestive heart failure.[58]

Abbreviations: CHF=congestive heart failure; NYHA=New York Heart Association

Nursing Staff Satisfaction

None of the included studies reported on nursing staff satisfaction or their experience with the nurse-managed protocols.

Treatment Adherence

One study reported on treatment adherence,[74] finding that the intervention group improved self-care behaviors more than the control group (*p*=0.02) and retained the improved self-care behaviors after 12 months, while the control group did not. At 12 months, 79 percent of the intervention group continued to weigh themselves compared with 41 percent in the control group (*p*<0.01). Participants in the intervention group compared with control were also better at alerting the health care system about weight gain (74% vs. 38%, *p*<0.01) and restricting fluid intake (50% vs. 28%, *p*=0.07), respectively.

Quality Measures
Biophysical Markers

Mortality. All 10 RCTs, involving 2836 patients, reported effects on all-cause mortality and were included in the quantitative analysis (Figure 10). ORs for mortality were significantly lower in the intervention groups compared with controls (OR 0.71; 95% CI, 0.52 to 0.96), with moderately inconsistent treatment effects (Q=15.97, df=9, *p*=0.07; I^2=44%). Using the summary OR and median event rate from the control arm of the trials, we estimated the absolute treatment effect as a risk difference of 36 fewer deaths per 1000 patients (95% CI, 62 to 5 fewer). A funnel plot did not show evidence of publication bias (Appendix B).

We performed subgroup analyses to explore for differences in intervention effects between studies conducted in the United States compared with other countries, studies incorporating

self-management plans or specific behavioral interventions versus those that did not, and studies delivering the intervention primarily by clinic visits versus telephone interventions. There were no telephone-based studies and no statistically significant differences in treatment effects for any of the other subgroup analyses (Appendix G).

Figure 10. Effects of nurse-managed protocols on mortality

Study or Subgroup	Nurse Protocol Events	Total	Usual Care Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Angerman 2012	32	352	52	363	15.6%	0.60 [0.37, 0.95]	
Berger 2010	21	96	35	90	11.7%	0.44 [0.23, 0.84]	
DeBusk 2004	21	228	29	234	12.7%	0.72 [0.40, 1.30]	
Ekman 2003	18	70	15	75	9.4%	1.38 [0.64, 3.02]	
Giordano 2009	20	226	32	229	12.7%	0.60 [0.33, 1.08]	
Krantz 2008	0	24	1	23	0.8%	0.31 [0.01, 7.91]	
Mejhert 2004	40	103	34	105	13.2%	1.33 [0.75, 2.34]	
Sisk 2006	22	203	22	203	12.0%	1.00 [0.53, 1.87]	
Stromberg 2003	7	52	20	54	7.0%	0.26 [0.10, 0.70]	
Thompson 2005	5	58	7	48	4.9%	0.55 [0.16, 1.87]	
Total (95% CI)		1412		1424	100.0%	0.71 [0.52, 0.96]	
Total events	186		247				

Heterogeneity: Tau² = 0.10; Chi² = 15.97, df = 9 (P = 0.07); I² = 44%
Test for overall effect: Z = 2.26 (P = 0.02)

Favors Nurse Protocols   Favors Usual Care

Abbreviations: CI=confidence interval

Health-related quality of life (HRQOL). Four studies reported effects on general measures of HRQOL.[50,66,73,75] Two of these found significant effects on the SF-36 physical health component: Angermann et al.,[50] MD 2.1 (95% CI, 0.2 to 4.0), and Sisk et al.,[73] MD 3.1 (95% CI, 0.7 to 5.5). In a small study by Thompson et al.,[75] there was no statistically significant effect; however, the mean change in scores favored the intervention. In another study by Mejhert et al.,[66] there was no reported effect. Thus, limited evidence suggests that nurse-managed protocols may have a small positive effect on HRQOL.

Process-of-Care Measures

ACE/ARB-prescribing. Six of the 10 CHF-focused studies reported on the process measure of ACE/ARB-prescribing. Figure 11 shows the forest plot of the random-effects meta-analysis of nurse-managed protocols on the process measure of ACE/ARB-prescribing. Though statistically not significant, nurse-managed protocols were more likely to achieve target ACE/ARB-prescribing goals than usual care (OR 1.15; 95% CI, 0.90 to 1.46). Using the summary OR and median event rate from the control arm of the trials, we estimated the absolute treatment effect as a risk difference of 18 more ACE/ARB-prescribing goals reached per 1000 patients (95% CI, -15 to 45 more).

We performed subgroup analyses to explore for differences in intervention effects between studies conducted in the United States versus other countries, studies incorporating self-management plans or specific behavioral interventions versus those that did not, and studies delivering the intervention primarily by clinic visits versus telephone interventions. There were no telephone-based studies and no statistically significant differences in treatment effects for any of the other subgroup analyses (Appendix G).

Figure 11. Effects of nurse-managed protocols on ACE/ARB-prescribing goals
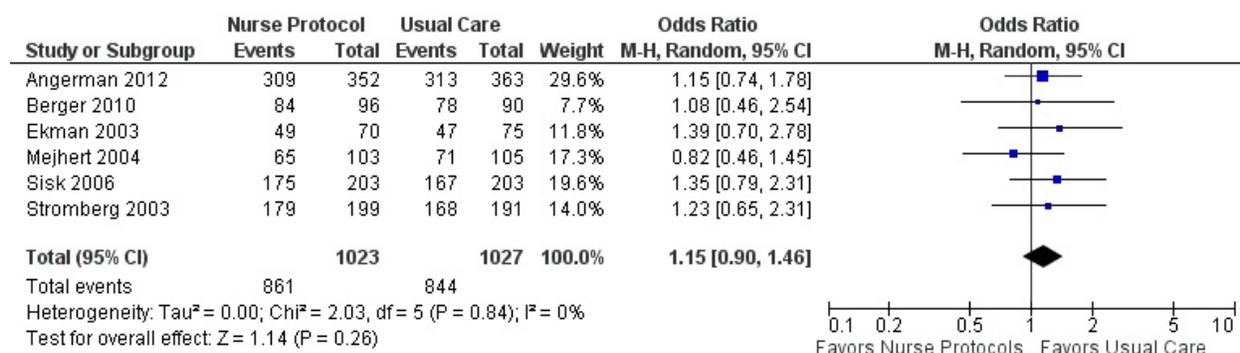
Abbreviations: ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocking; CI=confidence interval

Resource Utilization
Hospitalizations

Of the 10 studies conducted in patients with CHF, 7 RCTs (2538 patients) reported on hospitalization and were included in the quantitative analyses. Compared with usual care, nurse-managed protocols were associated with fewer total hospitalizations (OR 0.83; 95% CI, 0.62 to 1.10) (Figure 12) and fewer CHF-related hospitalizations (OR 0.62; 95% CI, 0.49 to 0.80) (Figure 13). Though results were overall not statistically significant (*p*=0.20) , one study did report a statistically significant decrease in days of hospitalization in the nurse-managed protocol group compared with control (1.4 vs. 3.9, *p*=0.02).[74]

Using the summary OR and median event rate from the control arm of the RCTs, we estimated the absolute treatment effect as a risk difference of 32 fewer total hospitalizations per 1000 patients (95% CI, CI, 76 fewer to 18 more) and 42 fewer CHF-related hospitalizations per 1000 patients (95% CI, CI, 57 to 22 fewer).

Subgroup analyses were conducted to explore for differences in intervention effects between studies conducted in the United States versus other countries, studies incorporating self-management plans or specific behavioral interventions versus those that did not, and studies delivering the intervention primarily by clinic visits versus telephone interventions. These analyses showed greater effects for studies that incorporated self-management plans or specific behavioral interventions on decreasing the number CHF-related hospitalizations (OR 0.47 vs. 0.75, *p*=0.04). Thus, nurse-managed protocols were associated with an overall decrease in hospitalizations, but effects varied. Exploratory subgroup analysis suggests some of the variability in intervention effects may be explained by intervention intensity and content (Appendix G).

Figure 12. Effects of nurse-managed protocols on total hospitalizations

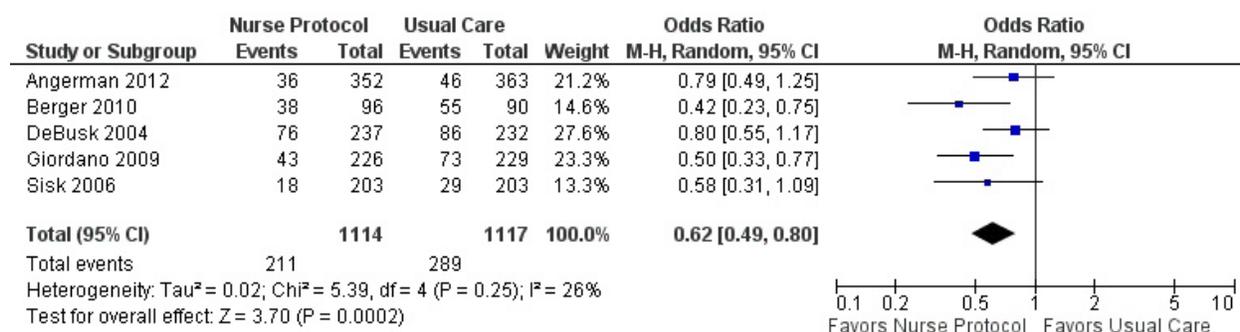| Study or Subgroup	Nurse Protocol Events	Total	Usual Care Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Angerman 2012	119	352	112	363	21.6%	1.14 [0.84, 1.57]
DeBusk 2004	116	228	117	234	19.8%	1.04 [0.72, 1.49]
Giordano 2009	67	226	96	229	19.0%	0.58 [0.40, 0.86]
Mejhert 2004	69	103	69	105	13.3%	1.06 [0.60, 1.88]
Sisk 2006	62	203	74	203	18.1%	0.77 [0.51, 1.16]
Thompson 2005	13	58	21	48	8.3%	0.37 [0.16, 0.86]
Total (95% CI)		**1170**		**1182**	**100.0%**	**0.83 [0.62, 1.10]**
Total events	446		489			

Heterogeneity: Tau² = 0.07; Chi² = 12.63, df = 5 (P = 0.03); I² = 60%
Test for overall effect: Z = 1.29 (P = 0.20)

Odds Ratio M-H, Random, 95% CI — Favors Nurse Protocol | Favors Usual Care

Abbreviations: CI=confidence interval

Figure 13 shows that CHF-related hospitalizations decreased significantly when nurse-managed protocols were used, with a consistent treatment effect. The study that reported total CHF-related hospital events (rate, not proportion) was not included in this analysis.[64] This study did find however that total heart failure rehospitalizations were reduced by 84% (3 vs. 19, *p* = .02).[64]

Figure 13. Effects of nurse-managed protocols on CHF-related hospitalizations

Study or Subgroup	Nurse Protocol Events	Total	Usual Care Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Angerman 2012	36	352	46	363	21.2%	0.79 [0.49, 1.25]
Berger 2010	38	96	55	90	14.6%	0.42 [0.23, 0.75]
DeBusk 2004	76	237	86	232	27.6%	0.80 [0.55, 1.17]
Giordano 2009	43	226	73	229	23.3%	0.50 [0.33, 0.77]
Sisk 2006	18	203	29	203	13.3%	0.58 [0.31, 1.09]
Total (95% CI)		**1114**		**1117**	**100.0%**	**0.62 [0.49, 0.80]**
Total events	211		289			

Heterogeneity: Tau² = 0.02; Chi² = 5.39, df = 4 (P = 0.25); I² = 26%
Test for overall effect: Z = 3.70 (P = 0.0002)

Odds Ratio M-H, Random, 95% CI — Favors Nurse Protocol | Favors Usual Care

Abbreviations: CI=confidence interval

Emergency Department (ED) Visits

ED visits were reported in two studies.[55,73] No performance metrics for ED visits were reported. Debusk et al.[55] reported virtually no differences between the number of patients in the intervention (55%) and control (56%) who were admitted to the ED (*p*>0.05). The study by Sisk et al.[73] reported similar results with no difference in ED admissions in the nurse-managed protocol intervention group (33%) compared with the usual care group (37%) (*p*>0.05). Further, there was no significant difference in patients having more than one ED visit between the two groups (MD -5.7; 95% CI, -15.0 to 3.7).

Total Costs

Only one study reported costs of the nurse-managed protocol interventions.[61] Mean cost for hospital readmission was significantly lower (-35%) in the intervention group (€843 ± 1733) compared with the control group (€1298 ± 2322; *p*<0.01).

Studies Targeting Older Patients With Chronic Conditions

One study by Dorr, et al.[58] targeted older patients (mean age = 76.2 years) with chronic conditions who had a combination of diabetes, hypertension, and CHF. This low-quality non-RCT of 3432 patients who were 96% white and 64.6% female used a disease-management program where an RN-equivalent used a protocol to titrate medications and deliver additional behavioral self-management and education in primary care clinics. Outcomes were reported at 12 and 104 months with a focus on mortality and resource utilization. Mortality was significantly lower at 12 months in the intervention compared with control (6.2% vs. 10.6% deaths, $p<0.05$). Total and CHF-related hospitalization rates were lower yet not significant at 12 months. At 2-year mortality, total and CHF-related hospitalizations continued to be lower though not significantly. However, ED visits increased in the nurse-managed protocol group compared with control, also not significant.

KEY QUESTION 2. In studies of nurse-managed protocols, how well do participating nurses adhere to the protocol?

Key Points

- Indirect evidence (e.g., improved outcomes) suggests that nurses adhere to protocols, but direct evidence (e.g., through fidelity checks) is insufficient to establish how well nurses adhere to protocols when engaged in delivering nurse-managed care.
- Only two of 29 included studies reported increased nurse adherence to treatment protocols.

Indirect evidence suggests that nurses adhere to protocols. Results from increased ACE/ARB treatment goals suggest nurses used the protocols. Two studies[49,70] reported data on adherence to treatment protocols. When compared with usual care, nurses instituted pharmacological therapy for lipid management more often.[49] DeBusk et al.[70] reported that hypoglycemic agents and antihypertensives including ACE inhibitors, angiotensin 2 antagonists, and statins were started or doses increased by nurses following treatment protocols compared with usual care groups. However, there was no report of fidelity to the protocols (e.g., levels of titration, consultation with a supervisor). Thus, the data is insufficient to establish how well nurses adhere to protocols when engaged in delivering nurse-managed care.

KEY QUESTION 3. Are there adverse effects associated with the use of nurse-managed protocols?

Key Points

- Adverse events were reported in only one study.
- Evidence was insufficient to establish if there are adverse effects associated with the use of nurse-managed protocols.

There was a paucity of reported adverse events in the included studies (for details on mortality, refer to section above). Adverse events include, for example hypoglycemic or syncope episodes

due to medication titration, wrong medications or dosage prescribed, drug-to-drug interactions, development of renal failure, or increased rates of injury such as falls. Only one fair-quality U.S. study on diabetes in a health maintenance organization by Aubert et al.[51] reported on adverse events. Severe low blood glucose events were identical (1.5%) at baseline and increased similarly, 2.9% in the control group compared with 3.1% in the intervention group (*p*=0.158). Death did not occur in either group.

SUMMARY AND DISCUSSION

Steadily increasing costs of chronic disease care and reports of poor or inconsistent patient adherence with established chronic disease treatment regimens, combined with primary care clinician shortages, provided compelling impetus for exploring whether the use of nurse-managed protocols can increase access and improve chronic disease outcomes in the outpatient setting. In this systematic review, we explored the outcomes of 26 RCTs and 3 non-RCT observational studies with moderate to high quality that assessed the effects of nurse-managed care using disease-specific protocols compared with usual care. Patient populations included those with diabetes, hypertension, hyperlipidemia, and CHF. All studies used an RN or equivalent. There was no report of using an LPN. In these studies, nurse providers had the autonomy to titrate disease medications according to a structured algorithm or protocol. In most studies, nurses also delivered patient education, but other details such as the limits on scope of care and triggers for supervision often were not well described. Additional medication management and behavioral or self-care interventions were commonly part of the intervention. Care was delivered through in-person clinic visits and telemedicine. Study outcomes ranged from health-related quality of life to biophysical and economic outcomes. Findings and overall strength of study evidence are summarized below by KQ.

SUMMARY OF EVIDENCE BY KEY QUESTION

KQ 1: Effects of Nurse-Managed Protocols Compared With Usual Care

Studies were divided into two categories: those targeting patients with elevated cardiovascular risk (18 studies) and patients with CHF (10 studies). One additional study was conducted among a cohort of older adults with chronic conditions, which included a mixture of elevated cardiovascular risk and CHF. The majority of patients receiving nurse-managed protocol care had moderate disease (i.e., moderate hypertension or CHF).

The most robust finding is that nurse-managed protocols had a positive impact on the biophysical outcomes of chronically ill patients. Among the studies targeting elevated cardiovascular risk, HbA1c improved by approximately 0.4 percentage points (moderate strength of evidence [SOE]); systolic and diastolic blood pressure improved by 4 mmHg and 2 mmHg, respectively (moderate SOE); total cholesterol improved by 9 mmol/l, and LDL improved by 12 mmol/l (low SOE). Among the CHF studies, nurse-managed care resulted in a significant decrease in mortality and fewer CHF-related hospitalizations (high SOE). For both patient groups, nurse-managed protocols also were more likely to achieve target goals for markers of disease severity (e.g., lipid values) or medication-prescribing goals (moderate SOE).

Subgroup analyses showed some differences between in-person and telephone-based care studies, non-U.S. and U.S.-based studies, and among studies that incorporated self-management plans or specific behavioral interventions. Interventions delivered primarily by telephone showed significantly greater effects for total and LDL cholesterol in patients with elevated cardiovascular risk and greater mortality reductions in patients with CHF. There was a similar pattern for other outcomes but these were not statistically significant. These exploratory analyses suggest that

telephone-based care may be a promising delivery mode for implementing nurse-managed protocols. Other subgroup analyses did not show any consistent pattern across outcomes.

Patient treatment adherence was reported in 6 studies, and medication adherence was reported in only 1. Effects of nurse-managed protocols on lifestyle changes and medication adherence were reported infrequently, but when reported showed an overall pattern of small positive effects (low SOE). The strength of evidence was insufficient to estimate a treatment effect for all other outcomes: nurse satisfaction, health-related quality of life, and health care costs. Table 6 summarizes the strength of evidence for KQ 1.

Table 6. Detailed summary of the strength of evidence for KQ 1

Outcome	Number of Studies (Patients)	Study Design/ Risk of Bias	Consistency Directness	Precision Publication Bias	Effect Estimate (95% CI)	SOE
Strength of Evidence Domains						
Nurse-managed protocol intervention vs. usual care – cardiovascular risk studies						
Hemoblogin A1c	8 (2633)	RCT/Moderate	Inconsistent Direct	Precise None detected	MD = -0.40 (-0.63 to -0.17)	Moderate
Systolic blood pressure	12 (10,224)	RCT/Moderate	Inconsistent Direct	Precise Possible bias	MD = -3.68 (-5.67 to -1.69)	Moderate
Diastolic blood pressure	12 (10,224)	RCT/Moderate	Inconsistent Direct	Precise None detected	MD = -1.56 (-2.57 to -0.55)	Moderate
Blood pressure at goal	10 (9707)	RCT/Moderate	Inconsistent Direct	Precise None detected	OR = 1.41 (1.12 to 1.78) RD = 77 more per 1000 patients (24 to 133 more)	Moderate
Total cholesterol	9 (3494)	RCT/Moderate	Inconsistent Direct	Imprecise None detected	MD = -9.37 (-17.87 to -0.87)	Low
LDL cholesterol	6 (1119)	RCT/Moderate	Inconsistent Direct	Imprecise None detected	MD = -12.07 (-24.10 to -0.03)	Low
Cholesterol at goal	11 (9221)	RCT/Moderate	Inconsistent Direct	Precise None detected	OR = 1.54 (1.14 to 2.08) RD = 106 more per 1000 patients (33 to 174 more)	Moderate
Nurse-managed protocol intervention vs. usual care – congestive heart failure studies						
Mortality	10 (2836)	RCT/Low	Inconsistent Direct	Precise None detected	OR=0.71 (0.52 to 0.96) RD=36 fewer per 1000 patients (5 to 62 fewer)	Moderate
Total hospitalizations	6 (2352)	RCT/Low	Inconsistent Direct	Imprecise None detected	OR=0.83 (0.62 to 1.10) No significant difference: RD = 32 fewer per 1000 patients (76 fewer to 18 more)	Low
CHF-related hospitalizations	5 (2231)	RCT/Low	Consistent Direct	Precise None detected	OR=0.62 (0.49 to 0.80) RD=42 fewer per 1000 patients (22 to 57 fewer)	High
ACE/ARB prescribed	6 (2050)	RCT/Low	Consistent Direct	Imprecise None detected	OR=1.15 (0.90 to 1.46) No significant difference: RD = 18 more per 1000 patients (15 fewer to 45 more)	Moderate

Abbreviations: ACE=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CHF=congestive heart failure; CI=confidence interval; LDL=low-density lipoprotein; MD=mean difference; OR=odds ratio; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; SOE=strength of evidence

KQ 2: Adherence to Nurse-Managed Protocols

No studies reported fidelity to important elements of the treatment protocol. Indirect evidence (e.g., proportion of patients prescribed the indicated medication) suggests reasonable adherence to the medication elements of the protocol. Few studies (only 2) reported the type and amount of treatment protocol adherence. Though these studies demonstrated nurse protocol adherence by nurses in intervention groups compared with controls, the strength of evidence on adherence was judged to be insufficient.

KQ 3: Adverse Effects Associated With Nurse-Managed Protocols

The absence of reports of adverse effects in the studies is notable. Only 3 (10%) of the 29 included studies reported adverse effects. In the one, adverse effects occurred at similar rates in both diabetes intervention and control groups. Given the minimal number of studies citing increases in adverse effects, the strength of evidence was judged to be insufficient to determine the impact of nurse-managed protocols on adverse effects in chronic disease treatment studies.

CLINICAL AND POLICY IMPLICATIONS

In 2010 the Veterans Health Administration began to implement the Patient Aligned Care Team, known as PACT. The goal of this initiative was to transform the VA health care delivery system to one that is increasingly patient-centered. PACTs focus on each Veteran working together with a team of health care professionals, family members, and caregivers to plan for whole-person care and wellness. The PACT model serves as an example of how a team-based approach can be used to improve the quality and efficiency of chronic disease care. Because effective management of chronic diseases can be time-intensive, costly, and involve both medical therapy and behavioral and self-management interventions, it is becoming increasingly important to involve a multidisciplinary team such as PACT. Coupled with the 2010 Patient Protection and Affordable Care Act—which is expected to generate an influx of patients into the U.S. health system—there is increasing demand for chronic illness care. Further, with an expanding U.S. population, the number of patients per physician is growing. As the largest segment of the health care workforce, nurses are ideally suited to collaborate with other professionals in meeting the increasing demand for chronic disease care. Nurses often work in interdisciplinary teams and oversee the integration of care by multiple providers, in addition to providing active oversight of patients' abilities to understand and comply with complex medical regimens.[77]

Systematic reviews and meta-analyses led by Clark et al.[32,33] found that nurse-led interventions have been shown to improve control of high blood pressure in people with diabetes (-5.8 mmHg),[33] and showed reductions in systolic blood pressure (-8.2 mmHg).[32] Further, results showed improved blood pressure in studies where the nurse used an algorithm to deliver care (-8.9 mmHg).[32] A Cochrane review indicated similar results.[37] Nurse-managed interventions by a heart failure specialist nurse reduced CHF-related readmissions after 12 months of followup and reduced all-cause readmission and all-cause mortality. While results from this meta-analysis and systematic review are consistent with prior literature, this review examined nurse-led interventions across multiple chronic illnesses and required the nurse to have the autonomy to titrate medication.

Our systematic review and meta-analysis suggest nurse-managed care using an RN with defined protocols and physician supervision to titrate medications may be promising for improving health outcomes among patients with chronic disease conditions. The finding that nurse-managed protocols have been implemented and evaluated in a variety of chronic conditions suggests that such interventions have an overall positive effect on health outcomes in patients with elevated cardiovascular risk. There is also preliminary evidence of a decrease in mortality and resource utilization in patients with CHF.

However, these results leave many questions unanswered. Clinical replication of these nurse-managed interventions would be difficult at this time. Protocols used were often incompletely described and often failed to report adherence to the protocol by the nurse and the extent to which the nurse actually utilized autonomy to titrate or prescribe medications. In some studies, telephone followup augmented clinic encounters. Few studies reported the mean number of contacts, and many did not explain the planned number of nursing contacts. While this lack is not uncommon,[78] it makes replication challenging. In addition, while all studies in this review required the nurse to have the autonomy to titrate medications, they did not all allow the nurse to prescribe new medications.

More detailed information is needed about the practice boundaries, training experience required, clinical knowledge needed, decisionmaking confidence, communication capacity, the best patient population to target, and supervision needed for safe and effective clinical care. Some of the studies used very experienced nurses with special certifications (e.g., diabetes-certified nurse). In the United Kingdom, nurses in a variety of positions are involved in the management of medication for patients with diabetes. Findings from a UK survey revealed that among 214 nurses with prescribing rights, more than 85 percent had undertaken specialist training in diabetes and had a wealth of clinical experience.[79] It is important to note that there was no evidence examining the role and implications of the LPN using nurse-managed protocols. Thus, we cannot make recommendations at this time on the use of LPNs in this expanded role. Also, studies overall targeted patients with mild to moderate symptom severity. Thus, complex or unstable patients may not be best suited for these kinds of nurse-managed interventions. Last, there were limited data on the impact of nurse-managed protocols on health-related quality of life; further research is needed.

Review results were also promising with regard to improving quality measures. However, we know little about the acceptability to patients and primary care providers as well as to members of the nursing staff. We do not know if patients prefer this novel, nurse-led model of care over the traditional disease management approach where the physician remains largely in charge and the nurse is assigned to give adjunctive care. Further, we do not know if the nurse would prefer this expanded scope of practice or what percentage of RNs without advanced practice credentials would be willing to accept this expanded role.

Nurse-managed protocols expand the legal scope of practice of the RN. The practice of nursing includes comprehensive assessments of physical, mental, and social aspects of human conditions. Nursing responsibilities may include physical exams, health histories, patient education and counseling, and coordination of care.[80] Nurses implement treatments and pharmacological interventions by persons authorized by state regulations. RNs delegate and supervise nursing care of non-RNs, which include LPNs.

A clinical nurse specialist (CNS) is an advanced practice registered nurse who has a master's degree in nursing and provides direct patient care. The scope of practice is based on the course of study completed. The primary focus of the CNS is improvement in patient outcomes and nursing care. The role also includes responsibilities for diagnosis and treatment of disease, and health promotion and prevention in individuals, families, and communities. However, the CNS does not diagnose and manage disease, prescribe medications, interpret or order laboratory tests, or make referrals. This is the role of the certified nurse practitioner.[81]

In many countries such as in the United Sates, the nursing scope of practice is regulated by a governing body such as a board of nursing. Therefore, before a general policy recommendation can be made in an existing health system, it would be prudent to ensure that the scope of expansion is in concert with the nursing scope of practice endorsed by the governing body.

If nurse-managed protocols were to be implemented in a health care system such as the VA, careful selection, training, and supervision of those nurses would be required. Detailed evidence-based protocols would need to be developed with specifics on the level of training, experience, and competency needed of the RN to be given autonomy to titrate medications. The protocol would also need to specify the targeted acuity of the patients, specific medications and scope of titration, and rules on reporting adverse events and patients status updates to a supervisor. A nurse-managed protocol would need to be piloted in selected clinics where a physician would choose to champion this new model of care and agree to supervise this expanded RN role. Also, because RNs have differing educational backgrounds and roles in the VA setting, a "phased-in" approach would be recommended, where nurse-managed protocols are tested first with experienced and even certified RNs.

Finally, we will need to think carefully about the role of physicians, nurse practitioners, physician assistants, and nurses in patient-centered medical home models of care. Specifically, if nurses are to assume an expanded role, will this eliminate nurses in the team with a traditional role? It is clear that we need to work in teams, but the proper role and skills or training needed for each profession must be fine-tuned. While assigning only the most complex patients to a physician and only the moderate or "less" sick patients to a nurse or advanced practice provider is possible, a balanced approach to responsibilities will be important to maintain staff satisfaction and prevent burnout—and to prevent confusion among patients and consumers on provider roles.[82]

STRENGTHS AND LIMITATIONS

Our study has a number of strengths, including a protocol-driven review, a comprehensive search, a careful quality assessment, and rigorous quantitative synthesis methods. Our report, and the literature, also has limitations. An important limitation is the lack of detailed description of the interventions and, in particular, the protocols the nurses used. There was limited reporting of the intensity of the intervention, treatment adherence by patients, protocol adherence by nurses, health-related quality of life, and resource utilization. Other performance measures of interest such as micro-albumin levels were rarely reported, and nursing staff satisfaction with the protocols was not reported. There also was limited reporting of the educational level and

supervision required of the nurses. Studies were limited to the use of an RN, and there was no report of using LPNs. Finally, the outcomes reported varied across studies and contributed to unexplained variability.

RECOMMENDATIONS FOR FUTURE RESEARCH

We used the framework recommended by Robinson et al.[83] to identify gaps in evidence and classify why these gaps exist (Table 7). This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps and classifies them as due to (1) insufficient or imprecise information, (2) biased information, (3) inconsistency or unknown consistency, and (4) not the right information. VA and other health care systems should consider their clinical and policy needs when deciding whether to invest in research to address gaps in evidence.

Table 7. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies to Consider
Patients		
Effects in patients with complex disease or multiple chronic conditions	Insufficient information	Single and multisite RCTs Quasi-experimental studies
Interventions		
Uncertainty about effects of narrowly focused (e.g., blood pressure) or multitarget (e.g., HbA1c, blood pressure, and lipids) interventions	Insufficient information Exploratory analysis suggests possible differential effect	RCTs or quasi-experimental studies of focused versus multi-target interventions
Interventions described in sufficient detail for replication	Insufficient information	Qualitative evaluation of nurse-managed protocols to address implementation needs of stakeholders
Uncertain level of training and supervision needed	Insufficient information	Job-skills analysis Survey of authors and nurse who have evaluated nurse-managed protocols
Outcomes		
Uncertain effects on patient and staff satisfaction and experience	Insufficient information	Nonrandomized or cluster randomized, multisite implementation studies, qualitative studies
Uncertain effects on adverse events	Insufficient information	Multisite observational studies
Uncertain effects on health system costs	Insufficient information	Costs analyses, particularly in patient group with elevated CV risk
Fidelity to the intervention protocol	Insufficient information	Quantitative and qualitative approaches as part of RCT or non-RCT trials or implementation studies
Uncertain whether there would be unintended consequences to other aspects of the health care system if nurse-managed protocols were implemented	Insufficient information	Multisite observational studies

Abbreviation: HbA1c=glycosylated hemoglobin; RCT = randomized controlled trial

Our review shows that nurse-managed protocols help to improve health outcomes among patients with moderate severity of diabetes, hypertension, hyperlipidemia, and CHF.

Studies overall targeted patients with mild to moderate symptom severity. Thus, further research is needed to understand the effects of nurse-managed protocols in complex or unstable patients.

To help guide the development and implementation of nurse-managed protocols, we recommend an exemplar VA quality improvement study conducted by Watts and colleagues (2011)[28] that provides detailed protocol descriptions but was not included in this report as it did not meet the Cochrane EPOC Guidelines for study designs. This project involved an internal training program for nurse case managers to improve glycemic outcomes for patients in the Cleveland Veterans Administration health care system. Existing nursing staff members were trained through weekly sessions to assume the role of a nurse case manager and encouraged to become certified diabetes educators. Nurses assumed the case management of patients with uncontrolled glycemic levels (HbA1c $\geq$9%). By following a detailed protocol, nurses were given authority to make referrals and to titrate insulin as prescribed by a primary care provider. Results indicated that, compared with usual care, nurse case managers achieved meaningful improvement in glycemic level control.

CONCLUSIONS

There is a pressing need to improve the medical management of adults with chronic disease, and our findings from this review of 29 studies justify testing nurse-managed protocols in the VA where detailed intervention components are monitored and data are collected. While there are many patient-level barriers that impede optimal treatment outcomes, the shortage of primary care clinicians in outpatient settings provides compelling justification to develop and test new models of chronic disease care. With the implementation of PACTs, the VA will play a critical role in reconfiguring team-based care models to expand the responsibilities of team members such as RNs to practice to the full extent of their education and training in order to improve outcomes for patients with chronic diseases.

As the largest health care workforce group, nurses are in an ideal position to collaborate with other team members in the delivery of more accessible and effective chronic disease medical care. Results from this systematic review and meta-analysis suggest that nurse-managed protocols have positive effects on the outpatient management of adults with stable, common chronic conditions such as type 2 diabetes, hypertension, hyperlipidemia, and CHF.

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APPENDIX A. SEARCH STRATEGIES

Table A-1. Search strategy for PubMed (December 12, 2012)

Set #	Terms	Results
1	"Nurse's Role"[Mesh] OR "Nursing Process"[Mesh] OR "Nursing Staff"[Mesh:noexp]) OR (nurse[tiab] OR nursing[tiab] OR nurses[tiab]	351362
2	(nurse[tiab] OR nursing[tiab] OR nurses[tiab]) AND (driven[tiab] OR intervention[tiab] OR interventions[tiab] OR managed[tiab] OR run[tiab] OR led[tiab] OR implemented[tiab] OR clinic[tiab] OR clinics[tiab])	43427
3	(nurse[tiab] OR nursing[tiab] OR nurses[tiab]) AND ("Diagnostic Tests, Routine"[Mesh] OR "Medication Therapy Management"[Mesh] OR "Referral and Consultation"[Mesh])	3585
4	(nurse[tiab] OR nursing[tiab] OR nurses[tiab]) AND (medication[tiab] OR drug[tiab] OR drugs[tiab]) AND (adjust[tiab] OR adjustment[tiab] OR manage[tiab] OR management[tiab] OR titrate[tiab] OR titration[tiab] OR prescribe[tiab] OR prescribing[tiab] OR initiate[tiab])	4080
5	(nurse[tiab] OR nursing[tiab] OR nurses[tiab]) AND ((order[tiab] OR ordered[tiab] OR ordering[tiab]) AND (diagnostic[tiab] OR test[tiab] OR tests[tiab]))	1168
6	#2 OR #3 OR #4 OR #5	48849
7	"Hypertension"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "Heart Failure"[Mesh] OR Hyperlipidemia[MeSH] OR Hypertension[tiab] OR Diabetes Mellitus[tiab] OR Heart Failure[tiab] OR hyperlipidemia[tiab]	764735
8	#1 AND #6 AND #7	2884
9	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])	4558979
10	"pre-post"[tiab] OR prepost[tiab] OR "post-test"[tiab] OR posttest[tiab] OR pretest[tiab] OR pre-test[tiab] OR quasi-experiment*[tiab] OR quasiexperiment*[tiab] OR quasirandom*[tiab] OR quasi-random*[tiab] OR quasi-control*[tiab] OR quasicontrol*[tiab] OR ("time-series"[tiab] AND interrupt[tiab]) OR ("time-points"[tiab] AND (multiple[tiab] OR one[tiab] OR two[tiab] OR three[tiab] OR four[tiab] OR five[tiab] OR six[tiab] OR seven[tiab] OR eight[tiab] OR nine[tiab] OR ten[tiab] OR month*[tiab] OR day[tiab] OR days[tiab] OR week*[tiab] OR hour*[tiab]) OR (before[tiab] AND after[tiab]) OR (*before[tiab] AND during[tiab]))	56936
11	(#8 AND (#9 OR #10) Publication date from 1980/01/01 to 2012/12/31, English	1822

APPENDIX B. ASSESSMENT OF PUBLICATION BIAS

Examination of ClinicalTrials.gov

We used our two main search term groups to search for clinical trials, type of nursing involvement, and disease of interest. For type of nursing, we investigated nurse's role (n=82), nurse-led protocols (n=13), nurse-managed protocols (n=79), nurse-led clinics (n=30) and nurse-managed clinics (n=136). "Nurse's roles" provided many off-topic entries. Appropriate entries under nurse-led protocols, nurse-managed protocols, and nurse-led clinics (all of which had significant overlap) were 100 percent contained under the key phrase "nurse managed clinics" or NMC. Therefore, we examined the entries found by the following combinations: NMC and diabetes (n=40), NMC and hypertension (n=14), NMC and congestive heart failure (n=19), and NMC and hyperlipidemia (n=3). Of the 76 entries produced by this search strategy, one entry overlapped in all categories, leaving 74 unique entries of which

- 38 were not completed

- 14 were not an intervention of interest (usually the nurse did not titrate medications)

- 7 expanded the role of a professional other than nurse although nurses were involved

- 5 had publications already identified in our database

- 4 were not from a country of interest

- 4 were not a population of interest

- 2 were not a disease of interest

Thus, we concluded there is no evidence of publication bias from our search of clinicaltrials.gov on May 30, 2013.

Funnel Plots

To detect possible publication bias, we produced funnel plots for outcomes reported by at least 10 studies. Plots and evaluation are presented here.

Figure B-1. Funnel plot for systolic blood pressure: indication of publication bias
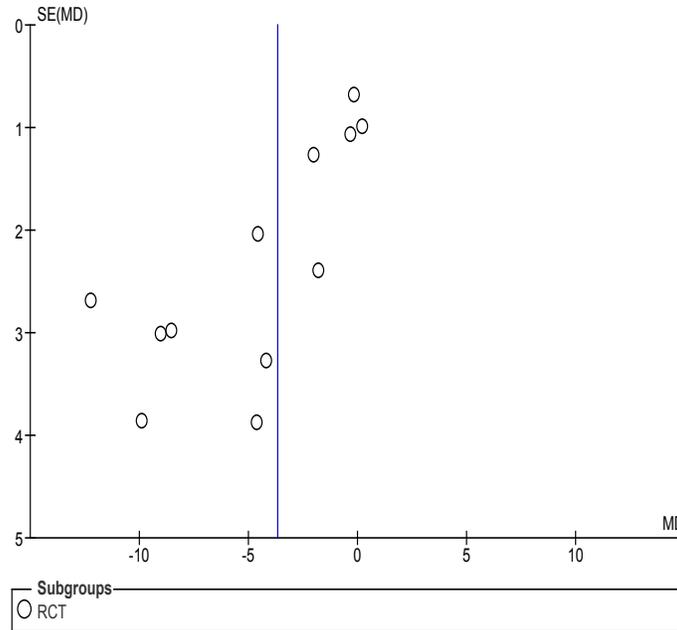
Figure B-2. Funnel plot for diastolic blood pressure: no indication of publication bias

Figure B-3. Funnel plot for cholesterol at goal: no clear indication of publication bias

Figure B-4. Funnel plot for blood pressure at goal: some asymmetry; no clear indication of publication bias

Figure B-5. Funnel plot for congestive heart failure mortality studies: no indication of publication bias
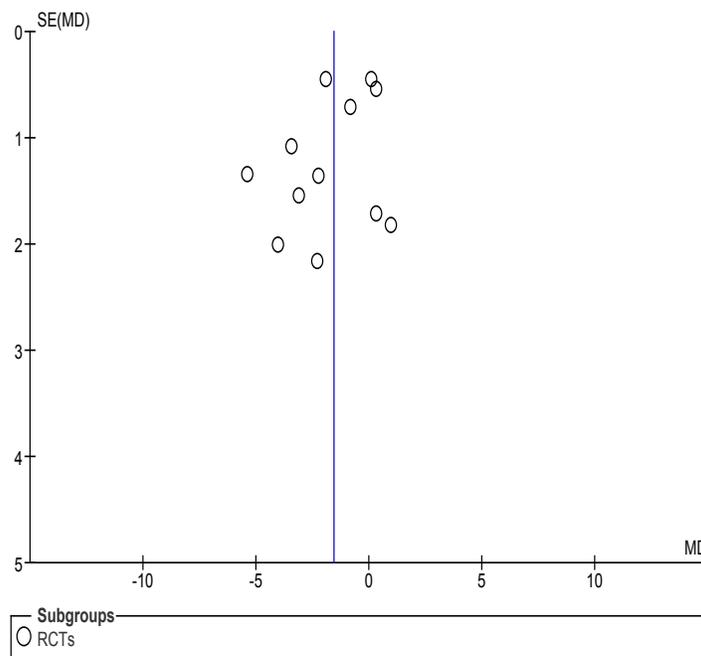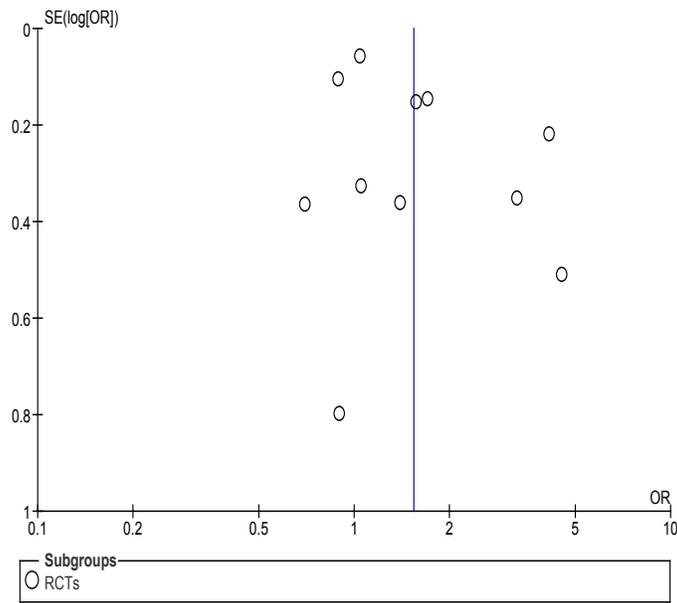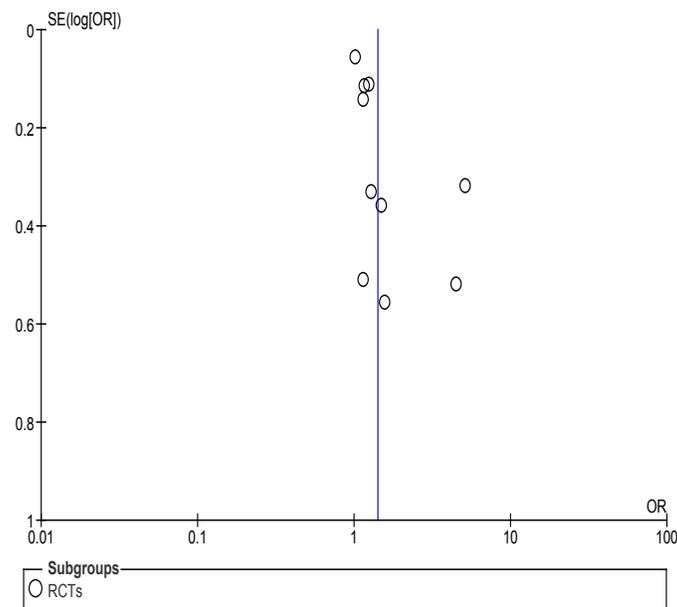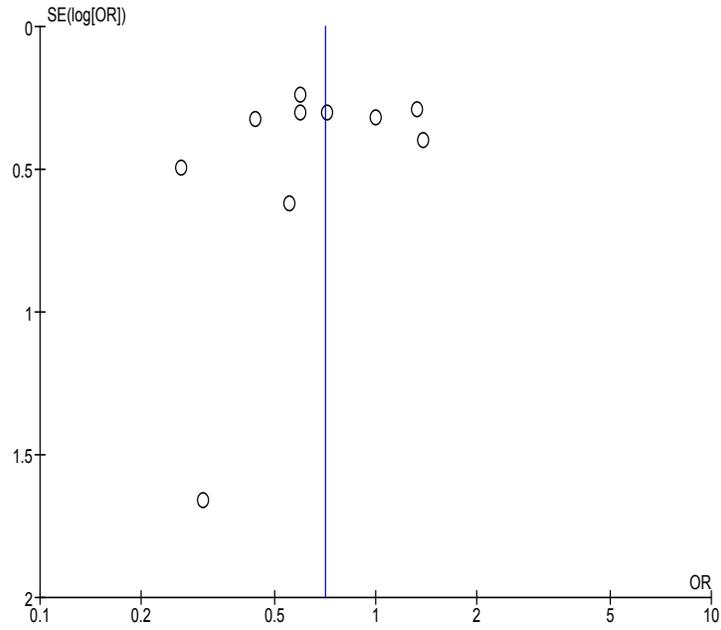
APPENDIX C. SAMPLE AUTHOR QUERY LETTER

Dear Dr. INSERT LAST NAME:

We are conducting a systematic review on **nurse-led interventions** and are writing in regards to your paper, "INSERT TITLE." To be eligible for our study, a) the intervention must utilize a nurse with similar training to a registered nurse or licensed practical nurse in the U.S.A. and b) the nurse must use a protocol to initiate or adjust one or more medications. Our preliminary review suggests your study is eligible for our review, but we require clarification about details of the intervention to make a final eligibility determination. Please answer the following:

1) Did the nurse(s) utilized in your study have similar educational training, credentials, or scope of practice to a Registered Nurse (RN) or Licensed Practical Nurse (LPN/LVN)? (see definitions below)

   a) Yes, similar to an RN or LPN

   b) Yes, similar to an RN or LPN but with the following important differences:_____

   c) No, not similar (e.g., equivalent to a U.S.A trained Advanced Practice Nurse)

2) Did the nurse use a protocol or algorithm to guide practice?

   a) Yes (We will appreciate if you share a copy of your nurse protocol. Please send by email)

   b) No

3) Did the nurse have decision making authority to initiate or adjust medications as specified in a protocol or algorithm?

   a) Yes, decision making authority

   b) No, the nurse did not initiate or adjust medications.

4) Additional clarification: (optional if other information is needed)

We sincerely appreciate your response to this query,

John W. Williams, MD, and Ryan Shaw, PhD, RN, for the Durham Evidence Synthesis Team

Description of **RN** or **LPNs** trained in U.S.A. (**ELIGIBLE** for our study)	Description of **Advanced Nurse Practitioners** (**NOT ELIGIBLE** for our study)
Education/training: • Diploma from a nursing school or hospital • Associate's degree in nursing (2-year degree) • Bachelor's degree in nursing (4-year degree)	**Education/training:** • Master's degree in nursing • Doctoral degree in nursing
Credentialing and Scope of Practice: • Educates patients, families, and communities on conditions and treatment plans • Assists and supports patients, families, and communities in performing lifestyle modifications • Provides emotional support to patients and their family • Monitors response to medical treatment plans • Administers medications and vaccinations • Monitors treatment adherence including medication compliance • Performs medication reconciliation • Helps perform diagnostic tests and analyzes results (i.e., blood sugar values and urine dipsticks) • Performs physical assessments including vital signs	**Credentialing and Scope of Practice includes the RN/LPN scope of practice and in addition:** • Prescribes medication and treatment • Orders and interprets diagnostic tests • Performs or assists in minor surgeries or procedures (e.g., biopsies, suturing, casting) • Can serve as a primary care provider • Includes nurse midwives, nurse anesthetists, clinical nurse specialists

APPENDIX D. CRITERIA USED IN RISK OF BIAS ASSESSMENT

I. Guidance on Assessing Risk of Bias for Randomized Controlled Trials

General instructions: (1) Rate each risk of bias item listed below as Low risk/ High risk/ Unclear risk (refer to Cochrane guidance to inform judgements). Add comments to justify ratings.
(2) After considering each quality item, give the study an overall rating of "Low risk," "Moderate risk," or "High risk" (see below).

<u>**Rating of individual items**</u>
* Indicates items contained in Cochrane Risk of Bias Tool.

1. **Selection bias:**
   a. <u>*Randomization adequate</u> (Adequate methods include random number table, computer-generated randomization, minimization without a random element.) **Low risk/ High risk/ Unclear risk**
   b. <u>*Allocation concealment</u> (Adequate methods include pharmacy-controlled randomization, numbered sealed envelopes, central allocation.) **Low risk/ High risk/ Unclear risk**
   c. <u>Baseline characteristics</u> (Consider whether there were systematic differences observed in baseline characteristics and prognostic factors between groups, and if important differences were observed, if the analyses controlled for these differences.) **Low risk/ High risk/ Unclear risk**

2. **Performance bias:**
   a. <u>*Concurrent interventions or unintended exposures</u> (Consider concurrent intervention or an unintended exposure (e.g., crossovers; contamination – some control group gets the intervention) that might bias results) **Low risk/ High risk/ Unclear risk**
   b. <u>Protocol variation</u> (Consider whether variation from the protocol compromised the conclusions of the study.) **Low risk/ High risk/ Unclear risk**

3. **Detection bias:**
   a. <u>*Subjects blinded</u> (Consider measures used to blind subjects to treatment assignment and any data presented on effectiveness of these measures.) **Low risk/ High risk/ Unclear risk**
   b. <u>*Outcome assessors blinded, hard outcomes</u> (Outcome assessors blind to treatment assignment for "hard outcomes" such as mortality.) **Low risk/ High risk/ Unclear risk**
   c. <u>*Outcome assessors blinded, soft outcomes</u> (Outcome assessors blind to treatment assignment for "soft outcomes" such as symptoms.) **Low risk/ High risk/ Unclear risk**
   d. <u>Measurement bias</u> (Reliability and validity of measures used.) **Low risk/ High risk/ Unclear risk**

4. **Attrition bias:**
   a. <u>*Incomplete outcome data</u> (Consider whether incomplete outcome data were adequately addressed, including systematic differences in attrition between groups [differential attrition]; overall loss to followup [overall attrition]; and whether an "intention-to-treat"

[ITT; all eligible patients that were randomized are included in analysis] analysis was performed.) (Note: mixed models and survival analyses are, in general, ITT.) **Low risk/ High risk/ Unclear risk**

5. **Reporting bias:**
   a. *Selective outcomes reporting (Consider whether there is any suggestion of selective outcome reporting; e.g., systematic differences between planned and reported findings.) **Low risk/ High risk/ Unclear risk**

Overall study rating

Please assign each study an overall quality rating of "Low risk," "High risk," or "Unclear risk" based on the following definitions:

A "**Low risk**" study has the least bias, and results are considered valid. A low risk study uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. [Items 1a and 1c; 2a; 3b and 3c; and 4a are all rated low risk.]

A "**Moderate risk**" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems (unclear risk). As the moderate risk category is broad, studies with this rating vary in their strengths and weaknesses. [Most, but not all of the following items are rated low risk: Items 1a and 1c; 2a; 3b and 3c; and 4a.]

A "**High risk**" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a high risk study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions. [At least one-half of the individual quality items are rated high risk or unclear risk]

Conflict of interest (recorded but not used as part of Risk of Bias Assessment)

Was there the absence of potential important conflict of interest? The focus here is financial conflict of interest. If no financial conflict of interest (e.g., if funded by government or foundation and authors do not have financial relationships with drug/device manufacturer), then answer "Yes." **Yes /No /Unclear**

II. Guidance on Assessing Risk of Bias for Nonrandomized Studies

This tool is intended to evaluate the quality of nonrandomized studies that assessed the outcomes of nurse-managed protocol interventions. Use this risk of bias tool for the following study designs: nonrandomized controlled trial, cohort studies, interrupted time series.

Instructions for use:

1. Items are organized by risk of bias domains (selection, performance, attrition, detection and reporting bias). Rate each question using the response categories listed. Focus on study design and conduct, not quality of reporting.

2. The first question, basic study design, is not used in the overall ratings but is collected for descriptive purposes.

3. After answering each item, rate the study overall as "low risk of bias," "moderate risk of bias," or "high risk of bias" based on the following definitions. This overall rating is specific to the basic study design used. For example, if the basic study design was a cohort study, then the risk of bias rating would be interpreted as "For a cohort study, the risk of bias is _____."

    A "**Low Risk of Bias**" study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses recruitment and eligibility criteria that minimizes selection bias; has a low attrition rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. These studies will meet the majority of items in each domain.

    A "**Moderate Risk of bias**" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid. These studies will meet the majority of items in most but not all domains.

    A "**High Risk of Bias**" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

1.   **Basic Design**

     Is the study design prospective, retrospective, or mixed? [*Abstractor: Prospective design requires that the investigator plans a study before any data are collected. Mixed design includes case-control or cohort studies in which one group is studied prospectively and the other retrospectively.*]

     Prospective   ☐

     Mixed   ☐

     Retrospective   ☐

     Cannot determine   ☐

2.   Selection Bias

2.1   Inclusion/exclusion criteria

Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?

    Yes (low risk of bias) ☐

    No (high risk of bias) ☐

    Cannot determine (unclear risk of bias) ☐

    NA: study does not include comparison groups ☐

2.2.   Recruitment:

Did the strategy for recruiting participants into the study differ across study groups?

    Yes (high risk of bias) ☐

    No (low risk of bias) ☐

    Cannot determine (unclear risk of bias) ☐

    NA (retrospective study design) ☐

2.3   Baseline characteristics similar or appropriate adjusted analysis

Are key characteristics of study participants similar between intervention and control groups? [Patients *Age, Race, Gender, Illness severity]* If not similar, did the analyses appropriately adjust for important differences?

    Yes (similar or appropriate adjusted analysis; low risk of bias) ☐

    Partially (only some characteristics described or some characteristics not clearly described; analysis adjust for some) ☐

    No (important baseline differences, unadjusted analysis; high risk of bias) ☐

2.4   Comparison Group

    Is the selection of the comparison group appropriate? [*Patients exposed to usual care or another quality improvement strategy is appropriate; if comparison group determined at the physician or practice level, the comparison groups should be drawn from the same system.*)

Yes (low risk of bias) ☐

No (high risk of bias) ☐

Cannot determine, no description of the derivation of the comparison cohort ☐
(unclear risk of bias)

NA (study does not include a comparison cohort - case series, one-arm study) ☐

2.5   Balance prognostic variables between groups through design or analysis approaches.

Any attempt to balance the allocation between the groups? [For example, through stratification, matching, propensity scores]

Yes (low risk of bias) ☐

No (high risk of bias) ☐

Cannot determine (unclear risk of bias) ☐

3.   Performance Bias

3.1   Intervention implementation

Did variation from the study protocol compromise the conclusions of the study *[Similar to a psychologist following a manualized procedure to deliver psychotherapy, the nurse-managed protocol intervention should be implemented as planned]*?

Unclear (no data reported on fidelity to protocol; unclear risk of bias) ☐

Low fidelity (few components of protocol implemented; high risk of ☐
bias)

High fidelity (all key components of protocol were implemented; low ☐
risk of bias)

3.2   Concurrent/concomitant interventions

Did researchers rule out any impact from a concurrent intervention, such as greater access to other specialty interventions or medications (e.g., through multivariate analysis, stratification, or subgroup analysis)?

Yes (low risk of bias) ☐

No or Partially (only some concurrent interventions eliminated; high ☐
risk of bias)

Not described (unclear risk of bias) ☐

4.   Attrition Bias

4.1   Equality of length of followup for participants

In cohort studies, is the length of followup different between the groups? *[Abstractor:
Where followup was the same for all study patients the answer is no. If different lengths
of followup were adjusted by statistical techniques, for example, survival analysis, the
answer is no. Studies where differences in followup are ignored should be answered yes.]*

    Yes (high risk of bias) ☐

    No (low risk of bias) ☐

    Cannot determine (unclear risk of bias) ☐

4.2   Completeness of followup

Was there a high rate of differential or overall attrition? *[Attrition is measured in relation
to the time between baseline (allocation in some instances) and outcome measurement.
Standard for overall attrition is <20 percent for <1 year f/u and <30 percent for longer
term ≥ 1 year). Standard for differential attrition is ≥ 10% absolute difference.]*

    Yes (high risk of bias) ☐

    No (low risk of bias) ☐

    Cannot determine (unclear risk of bias) ☐

4.3   Attrition affecting Participant Composition

Did attrition result in a difference in group characteristics between baseline and followup?

    Yes (high risk of bias) ☐

    No (low risk of bias) ☐

    Cannot determine (unclear risk of bias) ☐

4.4   Intention-to-treat analysis

Is the analysis conducted on an intention-to-treat (ITT) basis, that is, the intervention
allocation status rather than the actual intervention received? *[Abstractor: evaluate
whether the analysis takes into account loss to followup]*

    Yes (low risk of bias) ☐

    No (high risk of bias) ☐

    Cannot determine (unclear risk of bias) ☐

    Not applicable (retrospective study) ☐

5. **Detection Bias**

5.1 **Blind outcomes assessment**

Were the outcome assessors blinded to the intervention or exposure status of participants?

Yes (low risk of bias)

**No or not stated and outcome could be influence by knowledge of
exposure status (high risk of bias)**

NA (not an intervention study)

5.2 **Source of information re interventions/exposure**

Are interventions/exposures assessed using valid and reliable measures, implemented
consistently across all study participants?

Yes (low risk of bias)

No (high risk of bias)

**Cannot determine, measurement approach not reported (unclear risk of
bias)**

5.3 **Source of information re outcomes**

a. Are <u>primary outcomes</u> (e.g., biophysical measures, performance metrics, symptom/
functional status measures) assessed using valid and reliable measures and
implemented consistently across all study participants?

Yes (low risk of bias)

No (high risk of bias)

**Cannot determine, measurement approach not reported (unclear risk
of bias)**

b. Are confounding variables assessed using valid and reliable measures, implemented
consistently across all study participants? [Major potential confounders include: age,
gender, race, disease severity, overall burden of disease.]

Yes (low risk of bias)

No (high risk of bias)

**Cannot determine, measurement approach not reported (unclear risk
of bias)**

6.   **Reporting Bias**

Are the potential outcomes pre-specified by the researchers? Are all pre-specified outcomes reported? [Abstractor needs to identify all pre-specified, primary outcomes that should be reported in the study.]

Yes (low risk of bias)   ☐

No (at least 1 pre-specified outcome not reported; high risk of bias)   ☐

Primary outcomes not pre-specified (unclear risk of bias)   ☐

Tool based on: Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. AHRQ Methods for Effective Health Care [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK49468/.

APPENDIX E. PEER REVIEW COMMENTS

Reviewer	Comment	Response
Question 1: Are the objectives, scope, and methods for this review clearly described?		
1	Yes. I appreciated the focused and concise research questions that guided this review. The inclusion and exclusion criteria are well stated and the search was comprehensive in accordance with the design. The review process was thorough in all aspects, with sufficient narrative to support findings, data synthesis, and risk of bias and strength of evidence. As a reviewer, the careful attention to these details gave me confidence in the objectivity of the study and in the results.	Thank you.
2	Yes. No comments	Acknowledged
3	Yes. No comments	Acknowledged
4	No. No comments	Acknowledged
5	Yes. No comments	Acknowledged
6	Yes. No comments	Acknowledged
7	Yes. The overall scope of this project is to improve the care of patients with select chronic conditions (hypertension, hyperglycemia, hyperlipidemia, and congestive heart failure); the mechanism selected to achieve this goal is to expand the role of the nurse within the PACT by using nurse-managed protocols. The objectives, scope and methods are clearly described. However, it remains unclear as to how the inclusion and exclusion criteria were determined for the intervention studied. That limiting the study selection to protocols involving medication adjustment may enhance the validity and generalizability of the project is acknowledged. Nonetheless, given the complexity of chronic illness, multiple approaches are likely needed to achieve positive outcomes. Thus it would be beneficial for the reader to better understand why educational interventions and therapy evaluation studies were excluded, as these interventions can also be useful in the management of chronic illness. Finally, the rationale for using nurse satisfaction as an inclusion criterion is missing and could be a useful addition.	Thank you for the thorough comment. We agree that educational and therapy interventions are important in the management of chronic illness, and multiple systematic reviews have described this literature. Our stakeholders were interested in studies where nurses practiced beyond their typical scope of practice (e.g., medication titration). Thus, we included studies that required the nurse to have the ability to practice beyond their scope of practice and have at a minimum the autonomy to titrate/adjust medication. Studies were not excluded if they had an educational or therapy component but were required to also have this medication titration component. Nurse satisfaction was not an inclusion criteria but part of Key Question 1 to examine the effects of nurse-managed protocols. Otherwise eligible studies that reported any of the relevant outcomes (including nurse satisfaction) were included.

Reviewer	Comment	Response
8	No. Overall, this is a very well done evidence synthesis in a complicated area. There are a few areas where additional clarification is needed regarding the objectives, scope, and methods.	
	1) Better clarification is needed regarding how "nurse" is defined in this synthesis and the generalizability of findings to different types of nurses. Throughout the report, terms such as "non-NP nurses", "nurse-managed protocols", "RN and LPN", and "RN-based protocol interventions" are used. Each of these terms defines nurses differently. The inclusion/exclusion criteria state that the intervention had to involve an RN or LPN functioning beyond the usual scope of practice, but then later on we see that only RNs were included in the studies in the evidence base. The generalizability of the evidence base only to RNs should be made earlier on in the report. A stronger statement is also warranted in the conclusion noting that there was no evidence specifically examining the role of the LPN in nurse-managed protocols and the implications of this if considering expanding nurse-managed protocols for LPNs.	1) Thank you for the comment. We have made terminology for nurse more consistent throughout the manuscript. We have also specified that no studies reported using LPNs as nurse interventionists and have made a stronger statement in the discussion that there is no evidence specifically examining the role of the LPN.
	2) Additional clarification is also needed in the introduction section regarding nurse-managed protocols. A more formal definition and history/background of these protocols would be helpful to the reader in understanding the scope. While it is acknowledged that there are many variations on what this protocol entails, in its current form, it is left up to the reader to determine the definition based on the inclusion/exclusion criteria, description of the included articles, etc. Similarly, it is unclear why adjustment of medications is the only component of the nurse-managed protocol that was required as part of the inclusion criteria. Additional background on nurse-managed protocols may help clarify this.	2) We agree with the reviewer and have added a brief discussion of how protocols began in nursing and also provided a definition of protocol. We have further specified that these studies were limited to those that required the nurse to have the ability to practice beyond their scope of practice and have at a minimum the autonomy to titrate/adjust medication.
	3) Risk of Bias (Quality) and Strength of Evidence Assessment section discusses criteria for observational studies; however, key eligibility criteria include randomized controlled trial or quasi-experimental study. Clarification is needed for this discrepancy.	3) We included RCTs and quasi-experimental studies. In the section, "Risk of Bias (Quality) Assessment" we give major criteria for RCTs and quasi-experimental (observational) studies.
9	Yes. Objectives, scope and methods were described clearly, see p. 11	Thank you.
Question 2: Is there any indication of bias in our synthesis of the evidence?		
1	No. As noted above, the team was fully engaged in conducting a detailed and thorough review and used processes to mitigate bias to the extent humanly possible. The narrative supports these efforts in process and in research study review.	Acknowledged
2	No. Very clear discussion on Bias concerns of the reviewed studies	Thank you.
3	No. No comments	Acknowledged

Reviewer	Comment	Response
4	No. No comments	Acknowledged
5	No. No comments	Acknowledged
6	No. No comments	Acknowledged
7	Yes. The risk of bias was carefully addressed overall. However, one area that can potentially bias the findings and the applicability to the PACT setting lies in the lack of a consistent definition of the term, "nurse" and "nurse training" (e.g., Tables 3 & 4). The type and role of the nurse was not well defined in the studies used for this evidence synthesis. For example, many of the studies were conducted in the U.K., using "specialist" nurses. The UKCC definition of specialist nurse in the UK appears more closely resembling that of the clinical nurse specialist in the U.S. than that of the registered nurse (see Standards for Specialist Education and Practice1). Other roles included certified diabetes educator (e.g., papers authored by Philis-Tsimikas, Aubert, Houweling,), "nurse specialist" in a particular disease, such as diabetes or CHF (e.g., papers by MacMahon Tone, O'Hare, Bellary, Wallymahmed, Berger), or "case manager" (e.g., papers by DeBusk, DeBusk); a rapid review of these papers did not find thorough descriptions of these roles nor of the educational preparation needed to qualify for such roles.	Thank you for the comment. We have made terminology for nurse more consistent throughout the manuscript. We have also specified that no studies reported using LPNs as nurse interventionists and have made a stronger statement in the discussion that there is no evidence specifically examining the role of the LPN. We have also added detail in Tables 4 and 5 (formerly Tables 3 and 4) under nurse training. Furthermore, we have included an appendix and additional description about querying authors when we were unsure of the educational role of the nurse. Authors for all included studies responded that the nurse interventionists used were a U.S.-equivalent RN.
7	Caution should be emphasized when generalizing these interventions to settings using nurses without such educational preparation and experience, and warrants more careful discussion early in the review. This concern is partially addressed in the clinical implications section (page 42), but given the importance, it warrants inclusion in the section describing the interventions (Tables 3 & 4), as well as in the executive summary. Perhaps additional information related to the role of the nurse in question and relevant educational preparation was obtained during the investigators' author query; if so, further delineation of role and educational preparation/training would help the reader.	Details on the education and preparation needed for a nurse to assume a responsibility to titrate medications is a gap in the literature (Table 2), noted as a limitation, and further research is warranted. We have added a key point to the executive summary that educational preparation was not well reported.
8	No. No comments	Acknowledged
9	No. Multiple sources of bias in the STUDIES reviewed were addressed and considered in the interpretation of the findings	Acknowledged
Question 3: Are there any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?		
1	No. The dominance of physician's leading all aspects of the health team through medical orders is not a surprise; it is surprising that there is so little in the research literature to support the autonomous contributions of other health professionals who spend considerably more time with patients. Given the era of evidenced-based practice, which grew out of care maps and other designs to manage patient care on a specified trajectory, it is equally distressing that the resources expended on those efforts has not been captured in the literature. My strong sense is that you have captured the state-of-research for these common health conditions.	Acknowledged

Reviewer	Comment	Response
2	No. I am aware that Portland VA Medical Center initiated some Nurse Run Protocols for initiation of insulin management and also hypertension. I do not know if there was any intent to publish as the protocols were not subject to the research disclaimers typically communicated.	Acknowledged
3	Yes. Comments: Watts, SA, Lawrence, RH, & Kern, E. (2011). Diabetes nurse care manager training program: enhanced care consistent with the chronic care and patient-centered medical home models. Clinical Diabetes, 29, 25-33. This VHA study found positive effects of nurses using diabetes protocols. This study addresses both the educational requirements for nurses as well as describing nurse satisfaction outcomes.	Thank you. We have added this study to the literature search numbers and added it to the discussion. This article by Watts, et al. (2011) will be quite useful as an exemplar for intervention descriptions, but it was not included in the report except in the Discussion as it did not meet the Cochrane EPOC Guidelines for study designs.
4	No. Not aware of any.	Acknowledged
5	No. No comments	Acknowledged
6	No. No comments	Acknowledged
7	No. A quick literature review did not reveal any substantive additional studies overlooked in this synthesis.	Acknowledged
8	No. No comments	Acknowledged
9	No. I am not aware of any that were omitted	Acknowledged
Question 4: Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
1	The VA – especially through the PACT model – should advance the role of nurses and other health professionals who are relevant to population health needs. The Advanced Practice Nurse who is prepared as a practice scholar (DNP) or a research scholar (PhD) is in the strongest position to develop, implement, and evaluate clinical protocols. These protocols should be evidence-driven and intersect with standard medical protocols for disease management. Nursing protocols should reflect the practice of nursing in that individual, family, and environmental/community needs should be included as part of a holistic approach. Behavioral protocols, reinforcement and motivation, and environmental adaptations should be clearly stated in interventional terms. The use of Registered Nurses to implement and evaluate approved protocols should be done once an assessment is made of the RNs clinical knowledge, decision-making confidence and adaptability, communication capacity (verbal and written) with patients, families, and health team members, and their capacity to be accountable. A well-rounded professional nurse will possess these qualities, but not all nurses possess these traits; some are most comfortable in a role where they are directed. Based on the review of the literature and the complexity of decision-science demanded to operate under protocol (regardless of how detailed), I would cautiously proceed with the use of an LPN in this role.	Thank you for this thorough comment. We agree that a well-rounded professional nurse will possess all the qualities to safely use nurse-managed protocols. However, because the studies included in this review did not use LPNs, we can only generalize the findings to that of the RN. We agree that further research is warranted as to the use of LPNs. We have added additional details regarding the need for more information on the clinical knowledge, decisionmaking confidence, and communication capacity needed for a nurse in this role.

Reviewer	Comment	Response
2	Appendix D, Page 65, took a while to find the explanations for the NLC and DMP abbreviations.	We have spelled out those terms (nurse-led clinic and disease management program) in the table cells. That table is now in Appendix F.
3	No comments	Acknowledged
4	No comments	Acknowledged
5	"All 29 studies required the nurse to have the autonomy to titrate medications; however, only 20 reported that the nurse was allowed to independently initiate a new medication." This review is excellent. Just one comment. I wonder about the use of the word "only" in the quote above. It implies that 20 is small portion but in fact it is actually 2/3rds of the sample. This is a small point but in our organization it has been extremely hard to get any action on this important health care delivery strategy. I would prefer to avoid any argument for those who find it hard to imagine using our excellent nursing colleagues in this way.	We have rewritten this section to simply describe that 20 of the 29 studies allowed the nurse to also prescribe medications in addition to titration.
6	No comments	Acknowledged
7	PACT embraces the concept of "team". The authors acknowledge the importance of the role of specific team members – physicians, nurse practitioners, physician assistants, and nurses (pg 43). The role of the LPN does not appear to fit within the body of evidence presented and warrants further description as to how the LPN role might still be utilized within the PACT model outside the scope of using nurse-managed protocols (pg 43). Clarifying what is meant by "nurses", including other nursing roles, such as the clinical nurse specialist and expanded-role registered nurse, would strengthen this comprehensive, high-quality evidence synthesis summary.	We have provided more detail that while our initial search included the use of LPNs, no studies used an LPN as the nurse interventionist. We generalize the findings to the RN and recognize that the absence of studies utilizing LPNs is a limitation of this review and warrants further research.
8	1) Page 23, first line in last paragraph under Treatment Adherence, it states "Among the studies that reported treatment adherence to medication"; however, earlier it was stated that only one study reported treatment adherence to medication. This inconsistency should be revised. 2) Not sure I agree with the conclusion that "Nurse-managed protocols may be most effective for managing illnesses where self-management and patient adherence to medications is needed," (pg. 8 and 44). Only one study directly examined patient adherence to medications; therefore, further support is needed to justify this conclusion.	Thank you noticing this. We have amended this inconsistency. We have revised this section to focus on using nurse-managed protocols where a nurse could titrate or prescribe important and frequently used medications for diseases such as diabetes where medication titration and self-management are both key.
9	No comments.	Acknowledged

Reviewer	Comment	Response
Optional Dissemination and Implementation Questions		
Question 5: Are there any clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.		
1	I believe this report could make a major contribution related to the IOM report, The Future of Nursing: Leading Change, Advancing Health and the Robert Wood Johnson Campaign for Action that is implementing major components of the IOM report. This report is germane to several key aspects of the report findings: expanded scope of practice, leadership development, testing new models of care, lifelong learning and expanding nurse competencies to meet the emerging public demands for access to care. Further, the implications for the process of developing nurses to assume expanded responsibilities should be observed and evaluated for sharing throughout the nursing community. There are many organizations who would benefit from the PACT model (I see this as part of model development) as the VA has defined the elements of the medical home.	Thank you.
2	Performance Measures exist for Diabetes Hemoglobin A1C > 9% or not done within a year, Cholesterol control in patients with Diabetes or Ischemic Heart disease, as well as hypertension. The hope is that appropriate Nurse run protocols can show improvement in these areas.	Acknowledged
3	Yes. The Office of Nursing Services is currently conducting several nurse protocol pilot programs in order to gather information to form national guidance. This report will be utilized in the formation of the national guidance	Acknowledged
4	No comments	Acknowledged
5	Absolutely, it provides the evidence to support revolutionizing how health care is delivered in the VA and will enable us to transform how care is delivered at every level of the organization. There will be no clinical service untouched.	Acknowledged
6	This will enhance our understanding and support utilization of nurse-managed protocols in PACT as well as specialty care transformation.	Acknowledged
7	Performance measures are currently described within this report as is PACT.	Acknowledged
8	No comments	Acknowledged
9	This review should inform the efforts in PACT to encourage nursing practice at the highest level of licensure. The data reviewed here also suggest some additional studies that would be appropriate to implement across sites using PACT, including the Centers of Excellence in Primary Care Education.	Acknowledged

Reviewer	Comment	Response
Question 6: Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.		
1	The question remains as to what a nurse-managed protocol looks like: how is it different than standing orders? How is it different from a care map? Is it designed to allow autonomy, or is it algorhymic in nature to avoid risk and to "catch" potentially weaker nurses by guiding them to a desired set of activities? This work should be done prior to implementation, or it will confound point-of-care providers as just another tool. So, it should LOOK different than other existing tools, should be LIMITED in scope to clinical conditions, and it must complement the reality that no patient has JUST one "chronic" medical condition – so the judgment tied to its use must place it within the context of the WHOLE patient medical portfolio of concerns.	We agree. There are a lot of details about nurse-managed protocols that are needed for next steps and implementation. Further investigation and translational research are needed.
2	If there are any hyperlinks to the study report themselves it would simplify getting more detail on what the specific protocols initiated were.	This is a good suggestion. Currently our reports are available only in pdf format, but we will pass the comment along to the ESP coordinating office.
3	Know the components that led to a successful intervention – such as hours and content of training, use of electronic medical record decision support, the development of clinical competency for evaluation.	We have included this information as recommendations for future research.
4	I thought that the satisfaction of the nursing staff listed first did not reflect a patient centered approach	Thank you for the comment. We agree that nurse satisfaction, while an important outcome, is not a patient-centered outcome. However, we present the results in the order listed in the Key Questions. Our executive summary, key points, and strength of evidence table focus on patient-centered and important biophysical outcomes.
5	See my comment in question # 4 above. "This may be particularly useful for diseases such as diabetes that have a preclinical phase in which the risk of complication is relatively high, or where medication titration and self-management are key to adequate management but symptoms are minimal or not yet clinically serious" I think this statement is speculative. We should stick to the evidence. My worry is that the elements in the VA who have been resisting this advance will latch on to this statement and slow our progress especially for those patients who are further along their disease progression and could therefore benefit in the short run. My recommendation would be eliminate this statement all together unless there is strong evidence that this is the only group where nurse protocols are effective.	Thank you. We have reworded this statement and moved away from the speculative phrasing.
6	Effective communication of the report findings will be valuable for facilitating implementation.	Acknowledged
7	See comments above for suggestions.	Acknowledged

Reviewer	Comment	Response
8	No comments	Acknowledged
9	Implementation of some of the protocols that were assessed in the studies reviewed would be facilitated by identification of links to the protocols, themselves, as well as translational work to be conducted within the VA sites, e.g. PACT and COE PCE sites	We agree. However, studies typically cited a guideline and gave only summary information about protocols. As part of our author queries, we requested copies of the protocol but the protocol was only provided by a single author. We highlighted the study by Watts et al. (2011), which gives detailed information about the protocol.
Question 7: Please provide us with contact details of any additional individuals/stakeholders who should be made aware of this report.		
1	Susan Hassmiller, RWJ Project Director – Campaign for Action; Mary Naylor – University of Pennsylvania – whose work with the transitional care model may be of assistance. Kathy Apple and Dr. Franklin Shaffer, with the National Council of State Boards of Nursing and Council on Graduates of Foreign Schools of Nursing, respectively, to guide their work.	Acknowledged
2	Dr. David Macpherson involved with Primary Care Field Advisory Committee. David.Macpherson@va.gov	Acknowledged
3	ONS will want to distribute this widely. PCS, including PACT, Specialty care and PBM should be made aware of the report	Acknowledged
4	Tri Council members, Diane Mancino, Debra Barksdale	Acknowledged
5	I think nursing service will be very receptive to these findings. Our greatest challenge will be with the specialty community and especially the specialist from a prior generation and/or who have not worked outside the VA. I would spend some informal time with the leaders of specialty care operations to solicit their support before distributing this review widely.	Acknowledged
6	In addition to PACT/Primary Care and Nursing, would also involve Specialty Care and Geriatrics.	Acknowledged
7	Marthe Mosley, PhD, RN, CCNS, Associate Director, Clinical Practice; Christine Engstrom, PhD, CRNP, Director, Clinical Practice, Storm Morgan, BSN, RN, MBA, ONS PACT Program Manager; Office of Nursing Service, Field Advisory Committees (cardiovascular, diabetes/ metabolic)	Acknowledged
8	No comments	Acknowledged
9	This is a timely and important study that should be circulated widely within and outside of the VA. Many of the protocols that were tested would most likely be appropriate for implementation within the Federally Qualified Health Centers and Nurse Managed Clinics, both of which have organizational structures to facilitate exchanges of information and findings in this report.	Acknowledged

APPENDIX F. STUDY CHARACTERISTICS TABLE

Table F-1. Characteristics of included studies

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Cardiovascular risk factors: Diabetes						
Aubert, 1998[1]	Florida, USA Primary care clinics Private system 138 randomized, 100 completed	Median age (IQR) Intervention group: 53.0 (47.0 to 61.0) Usual care: 54.0 (46.0 to 60.0) Female, grand mean for total: 60.2 Race/ethnicity, grand mean for total: White 76.5	Diabetes, mixed type 1 and 2 HbA1c> 7%	12 months • A1c • Blood pressure • Total and LDL cholesterol	Intervention Nurse-led clinic + team care for glucose run by RN+ST including education Comparator Usual care	RCT Moderate risk of bias, fair quality
Bellary, 2008[2]	Western Europe Primary care clinics National Health System, UK 1486 randomized, 1486 completed	<Age 45: 14% Age 45–65: 56% >Age 65: 30% Total female: 47.7 Race/ethnicity: NR	Diabetes, all type 2 Severity: NR	Every 2 months for 20 months • A1c • Blood pressure • Total cholesterol • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by RN+ST including education Comparator Usual care	RCT Low risk of bias, good quality

Fischer, 2012[3] (Fischer, 2008[4])	Colorado, USA
	
	Primary care clinic
	
	US Government
	
	762 randomized, 762 completed
		Age, grand mean for total (SD): 58.4 (NR)
		
		Female, grand mean for total: 61.0
		
		Race/ethnicity, grand mean for total:
		   Black 3.3
		   Hispanic 81.4
		   White 13.5
		   Other 2.0
			Diabetes, type NR
			
			Creatinine <3.0 mg/dL
				20 months
				
				• A1c
				• Total and LDL cholesterol
				• Performance measure
					Intervention
					Disease management program for glucose, blood pressure, and lipids run by RN+ST including education and self-management
					
					Comparator
					Usual care
						RCT
						
						Low risk of bias, good quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Houweling, 2009[5]	Western Europe Primary care clinics Netherlands 95 randomized, 84 completed	Age, grand mean for total (SD): 61.4 (NR) Female, grand mean for total: 53.3 Race/ethnicity: NR	Diabetes, all type 2 Severity: NR	12 months • A1c • Blood pressure • Total and LDL cholesterol • HRQOL • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, lipids run by nurse Comparator Usual care	RCT Moderate risk of bias, fair quality
Houweling, 2011[6]	Western Europe Primary care clinics Netherlands 230 randomized, 206 completed	Age, grand mean for total (SD): 60.0 (NR) Female, grand mean for total: 52.4 Race/ethnicity: NR	Diabetes, all type 2 Severity: NR	14 months • A1c • Blood pressure • Total cholesterol • HRQOL • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by RN+ST including education Comparator Usual care	RCT Low risk of bias, good quality
Cardiovascular risk factors: Diabetes with hypertension and hyperlipidemia						
MacMahon Tone, 2009[7]	Western Europe Hospital-based diabetes care clinic Ireland 200 randomized, 188 completed	Age, grand mean for total (SD): 61.7 (NR) Female, grand mean for total: 46.0 Race/ethnicity: NR	Diabetes, type 2 (with hypertension and hyperlipidemia) Total cholesterol >4.8 mmol/L, LDL >2.6 mmol/L, or blood pressure >130/80 mm Hg	12 months • Behavioral adherence • Performance measure • A1c • Blood pressure • Total and LDL cholesterol	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by specialist nurse including education Comparator Usual care	RCT Moderate risk of bias, fair quality
Meulepas, 2008[8]	Western Europe Primary care clinics Government (not US) 993 randomized, 900 completed (non-RCT)	Age, grand mean for total (SD): 69.5 (NR) Female, grand mean for total: 53.5 Race/ethnicity: NR	Diabetes, type 2 (with hypertension and hyperlipidemia) Severity: NR	36 months • Behavioral adherence • Performance measure • A1c • Total cholesterol	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by nurse including education Comparator Concurrent usual care: Active recall of patients on central diabetes registry	Non-RCT Moderate risk of bias, fair quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
New, 2003[9] (Mason, 2005[10])	Western Europe Shared care clinic National Health System, UK Randomized: 1014 in hypertension group and 683 in hyperlipidemia group Completed: 835 in hypertension group and 627 in hyperlipidemia group	Median age (IQR) Hypertension group: 63.5 (55.4 to 72.1) Usual care: 63.7 (56.4 to 71.9) Hyperlipidemia group: 56.5 (45.1 to 66.9) Usual care: (56.4 to 71.9) Female, grand mean for total: hypertension group, 50.0; hyperlipidemia group, 50.0 Race/ethnicity: NR	Diabetes, type NR (with hypertension and hyperlipidemia) SBP ≥140 or DBP ≥80 mmHg or total cholesterol ≥5.0 mmol/L	Mean intervention length 2.5 months, mean followup 18 months • Blood pressure • Total cholesterol • Performance measure	Intervention Nurse-led clinic for blood pressure and lipids run by specialist nurse including education and self-management Patients seen every 4 to 6 weeks for 30- to 45-minute appointments until targets achieved Comparator Usual care	RCT Moderate risk of bias, fair quality
New, 2004[11]	Western Europe Primary care clinics General practices in Salford, UK 10,303 randomized, 9977 completed	Cluster RCT of 44 practices in UK National Health Service Patient-level demographics NR	Diabetes, type NR with hypertension and hyperlipidemia) Blood pressure >140/80 mmHg or total cholesterol >5 mmol/L	24 months • Blood pressure • Total cholesterol • Performance measure	Intervention Nurse-led clinic + education outreach for blood pressure and lipids run by specialist nurse including education and behavioral Comparator Reverse control: 2-arm study where other intervention was control and vice versa	RCT Moderate risk of bias, fair quality
Philis-Tsimikas, 2004[12]	California, USA Primary care clinics US Government 290 randomized, 229 completed (non-RCT)	Age, grand mean for total: 50.5 (NR) Female, grand mean for total: 68 Race/ethnicity: NR	Diabetes, type 2 (with hypertension and hyperlipidemia) HbA1c >9%	12 months • A1c • Blood pressure • Total cholesterol • Performance measure	Intervention Nurse-led clinic + peer for glucose, blood pressure, and lipids run by RN+ST including education and self-management Comparator Concurrent usual care	Non-RCT High risk of bias, poor quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality

Taylor, 2003[13]	California, USA
	
	Primary care clinic
	
	Private system
	
	169 randomized, 127 completed
		Age, grand mean for total: 55.2 (NR)
		
		Female, grand mean for total: 47.5
		
		Race/ethnicity, grand mean for total:
		  Black 8.0
		  Hispanic 18
		  White 62.0
		  Other 12.0
			Diabetes, type 1 and 2 (with hypertension and hyperlipidemia)
			
			HbA1c >10%
				12 months
				
				• A1c
				• Blood pressure
				• Total and LDL cholesterol
				• Performance measure
					Intervention
					Disease management program + group education for glucose, blood pressure, and lipids run by RN+ST including education and self-management
					
					Comparator
					Usual care
						RCT
						
						Moderate risk of bias, fair quality

Wallymahmed, 2011[14]	Western Europe Diabetes center United Kingdom 81 randomized, 78 completed	Age, grand mean for total: 34.7 (NR) Female, grand mean for total: 44.5 Race/ethnicity: NR	Diabetes, type 1 (with hypertension and hyperlipidemia) HbA1c ≥8%	24 months • A1c • Blood pressure • Total and LDL cholesterol • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by RN+ST including education Comparator Usual care	RCT Moderate risk of bias, fair quality
Cardiovascular risk factors: Diabetes with hypertension						

Bebb, 2007[15]	Western Europe
	
	Primary care clinics
	
	National Health System, UK
	
	1534 randomized, 1420 completed
		Age, grand mean for total: 64.3 (NR)
		
		Female, grand mean for total: 41.0
		
		Race/ethnicity, grand mean for total:
		  White 90.5
		  Other 9.5
			Diabetes, type 2 (with hypertension)
			
			None
				12 months
				
				• Blood pressure
				• Performance measure
					Intervention
					Nurse-led clinic + algorithm implemented for blood pressure run by RN+ST
					
					Comparator
					Usual care
						RCT
						
						Moderate risk of bias, fair quality

Denver, 2003[16]	Western Europe
	Outpatient clinic
	
	Hospital-affiliated, United Kingdom
	
	120 randomized, 120 completed
		Age, grand mean for total: 61.2 (NR)
		
		Female, grand mean for total: 36.7
		
		Race/ethnicity, grand mean for total:
		  White 39
		  Other 61
			Diabetes, type 2 (with hypertension)
			
			BP >140/80 mmHg
				6 months
				
				• A1c
				• Blood pressure
				• Total cholesterol
				• Performance measure
					Intervention
					Nurse-led clinic for blood pressure run by nurse including education
					
					Comparator
					Usual care
						RCT
						
						High risk of bias, poor quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
O'Hare, 2004[17]	Western Europe Primary care clinics General practices 361 randomized, 325 completed	Total age: 58.8 (11.7) Total female: (49.0) Race/ethnicity: Other:100	Diabetes, type 2 (with hypertension) HbA1c >7%, SBP >140, DBP >80 mmHg, total cholesterol >5 mmol/L	12 months • A1c • Blood pressure • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by nurse including education and self-management Comparator Usual care	RCT Moderate risk of bias, fair quality
Cardiovascular risk factors: Hypertension						

Rudd, 2004[18]	California, USA
	
	Primary care clinics
	
	Private system
	
	150 randomized, 137 completed
		Age, grand mean for total (SD): 61.2 (NR)
		
		Female, grand mean for total: 36.7
		
		Race/ethnicity, grand mean for total:
		    White 39
		    Other 61
			Hypertension
			
			SBP >140 mm Hg or DBP >90 mm Hg
				6 months
				
				• Blood pressure
					Intervention
					Disease management program for blood pressure run by care manager including education, behavioral, and self-management
					
					Comparator
					Usual care
						RCT
						
						Low risk of bias, good quality

Cardiovascular risk factors: Hyperlipidemia						
Allison, 1999[19]	Minnesota, USA Cardiac rehabilitation center University-affiliated 195 randomized, 152 completed	Total age (SD): 64.0 (11.0) Total female: (18.0) Race/ethnicity: NR	Hyperlipidemia Severity: NR	17 months • Total and LDL cholesterol • Protocol adherence • Behavioral adherence • Performance measure	Intervention Nurse-led clinic for lipids run by RN+ST including education, behavioral, and self-management Comparator Usual care	RCT Moderate risk of bias, fair quality
DeBusk, 1994[20]	California, USA Single site (not reported) Private system 585 randomized, 425 completed	Age, grand mean for total (SD): 57.0 (NR) Female, grand mean for total: 21.3 Race/ethnicity, grand mean for total: White 77	Hyperlipidemia Severity: NR	12 months • Total and LDL cholesterol • Behavioral adherence	Intervention Disease management program for lipids run by RN+ST including education and self-management Comparator Usual care	RCT Moderate risk of bias, fair quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Congestive heart failure						
Angermann, 2012[21]	Western Europe 9 hospital-based call and care centers German health system 715 randomized, 567 completed	Age, grand mean for total (SD): 68.6 (NR) Female, grand mean for total: 29.4 Race/ethnicity: NR	CHF LVEF ≤40%	6 months • CHF mortality • HRQOL • Performance measure	Intervention Disease management program for CHF run by specialist nurse and including self-management; delivered by telephone Comparator Usual care	RCT Low risk of bias, good quality
Berger, 2010[22]	Western Europe Hospital clinics Vienna, Austria 278 randomized, 278 completed	Age, grand mean for total (SD): 72.0 (NR) Female, grand mean for total: 32.7 Race/ethnicity: NR	CHF NYHA class III or IV, cardiothoracic ratio >0.5 or LVEF <40%	12 months • CHF mortality	Intervention Disease management program for CHF run by specialist nurse and including education; delivered by telephone Comparator Multidisciplinary care or usual care	RCT Moderate risk of bias, fair quality

DeBusk, 2004[23]	California, USA
	
	Multisite (sites not reported)
	
	Private system
	
	462 randomized, 389 completed
		Total age (SD): 72.0 (11.0)
		
		Total female: (49.0)
		
		Race/ethnicity:
		  Black (5.8)
		  Hispanic (3.0)
		  White (84.0)
		  Other (7.6)
			CHF
			
			Severity: NR
				12 months
				
				• CHF mortality
					Intervention
					Disease management program for CHF run by care manager and including education, behavioral and self-management
					
					Comparator
					Usual care
						RCT
						
						Low risk of bias, good quality

Ekman, 2003[24]	Western Europe University hospital Gothenburg, Sweden 145 randomized, 108 completed	Age, grand mean for total (SD): 57.0 (NR) Female, grand mean for total: 15.1 Race/ethnicity: NR	CHF Boston criteria score ≥8 and NYHA class III or IV	1.5 months • CHF mortality • Performance measure	Intervention Nurse-led clinic for CHF by nurse including education; delivered by visit Comparator Usual care	RCT Moderate risk of bias, fair quality
Giordano, 2007[25]	Western Europe Telemedicine Italian hospitals and primary care clinics 460 randomized, 455 completed	Age, grand mean for total (SD): 80.0 (NR) Female, grand mean for total: 38.7 Race/ethnicity: NR	CHF Severity: NR	12 months • CHF mortality • Performance measure	Intervention Disease management program for CHF run by RN+ST; delivered by telephone Comparator Usual care	RCT Low risk of bias, good quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality

Krantz, 2008[26]	Colorado, USA
	
	Cardiology and diabetes clinic
	
	US public health care for vulnerable and indigent
	
	64 randomized, NR completed
		Age, grand mean for total (SD): 53 (NR)
		
		Female, grand mean for total: 31.2
		
		Race/ethnicity, grand mean for total:
		    Black 28.1
		    Hispanic 42.5
		    White 28.1
		    Other 1.6
			CHF
			
			LVEF ≤40%
				1 to 6 months of intervention; followup measurements at 2.5 and 6 months
				
				• CHF mortality
				• Performance measure
					Intervention
					Nurse-led clinic for CHF run by nurse specialist and including education; delivered by visit
					
					Comparator
					Usual care
						RCT
						
						Moderate risk of bias, fair quality

Mejhert, 2004[27]	Western Europe Hospital referral center University-affiliated 208 randomized, 208 completed	Total age (SD): 75.8 (7.1) Total female: (42.3) Race/ethnicity: NR	CHF LVEF ≤45% or atrioventricular plane displacement ≤10 mm	Intervention timeframe NR; 18 months of followup • CHF mortality • HRQOL	Intervention Nurse-led clinic for CHF run by nurse including education and self-management; delivered by visit Comparator Usual care	RCT Moderate risk of bias, fair quality

Sisk, 2006[28]	New York, USA
	
	4 hospitals in Harlem
	
	Not-for-profit institutions
	
	406 randomized, 406 completed
		Total age (SD): 59.4 (13.7)
		
		Total female: (46.3)
		
		Race/ethnicity;
		    Black (45.8)
		    Hispanic (32.5)
		    White (15.3)
		    Other (6.4)
			CHF
			
			LVEF <40%
				6 months of intervention; followup every 3 months for 1 year and at 18 months
				
				• CHF mortality
				• HRQOL
				• Performance measure
					Intervention
					Disease management program for CHF run by RN+ST including education and self-management; delivered mainly by telephone after initial assessment
					
					Comparator
					Usual care
						RCT
						
						Low risk of bias, good quality

Stromberg, 2003[29]	Western Europe Outpatient programs posthospitalization 3 hospitals and associated clinics, Sweden 106 randomized, 63 completed	Age, grand mean for total (SD): 77.5 (NR) Female, grand mean for total: 38.8 Race/ethnicity: NR	CHF NYHA class II to IV	12 months • CHF mortality • Behavioral adherence	Intervention Nurse-led clinic for CHF run by specialist nurse and including self-management including education and behavioral Comparator Usual care	RCT Low risk of bias, good quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Thompson, 2005[30]	Western Europe Nurse-led outpatient heart failure clinics National Health System, UK 106 randomized, 106 completed	Age, grand mean for total (SD): 72.5 (NR) Female, grand mean for total: 27.6 Race/ethnicity: NR	CHF LVEF <45%	6 months • CHF mortality • HRQOL • Performance measure • Medication adherence	<u>Intervention</u> Nurse-led clinic for CHF run by nurse including education and self-management; delivered by home visit <u>Comparator</u> Usual care	RCT Low risk of bias, good quality
Other eligible diagnosis						
Dorr, 2008[31]	Utah, USA Primary care clinics Private system 3732 randomized, 3732 completed (non-RCT)	Age, grand mean for total (SD): 76.2 (NR) Female, grand mean for total: 65.0 Race/ethnicity, grand mean for total: White 96	Age >65 years and complex medical presentation None	Mean 27 months • CHF mortality • Medication adherence • Hospitalizations • Emergency department visits	<u>Intervention</u> Disease management program for older adults run by RN+ST including education and behavioral <u>Comparator</u> Concurrent usual care	Non-RCT Low risk of bias, good quality

[a] Companion article is cited in parentheses where applicable.

[b] All interventions included nurse-titrated medication (by eligibility criteria) and patient education.

Abbreviations: CHF=congestive heart failure; DBP=diastolic blood pressure; HbA1c=glycosylated hemoglobin; HRQOL=health-related quality of life; IQR=interquartile range; LDL=low-density lipoprotein; LVEF=left ventricular ejection fraction; NR=not reported; NYHA=New York Heart Association; RCT=randomized controlled trial; RN+ST=nurse with study-specific training; SBP=systolic blood pressure; SD=standard deviation; UK=United Kingdom

REFERENCES CITED IN APPENDIX F

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APPENDIX G. SUBGROUP ANALYSES

Table G-1. Subgroup analyses[a,b]

Outcome	Non-US vs. US	Telephone vs. in-person	Single vs. multiple intervention target	Education with self-management or behavioral vs. not
Cardiovascular risk studies				
A1c (MD)	**-0.2 (I^2=34%) vs. -0.92 (I^2=0%) p=0.0003**	No studies in telephone group	**-1.1 (1 study) vs. -0.31 (I^2=55%) p=0.005**	-0.46 (I^2=84%) vs. 0.35 (I^2=16%) p=0.64
Systolic blood pressure (MD)	-3.24 (I^2=76%) vs. -6.55 (I^2=0%) p=0.17	-8.50 (1 study) vs. -3.27 (I^2=74%) p=0.10	-5.47 (I^2=85%) vs. -3.51 (I^2=74%) p=0.62	-2.12 (I^2=61%) vs. -5.86 (I^2=83%) p=0.15
Diastolic blood pressure (MD)	-1.58 (I^2=75%) vs. -1.49 (I^2=54%) p=0.96	-3.10 (1 study) vs. -1.46 (I^2=74%) p=0.31	-1.27 (I^2=63%) vs. -1.71 (I^2=73%) p=0.75	-1.36 (I^2=71%) vs. -1.99 (I^2=76%) p=0.62
Blood pressure performance measure (OR)	1.41 (I^2=77%) vs. 1.50 (1 study) p=0.87	No studies in telephone group	2.06 (I^2=84%) vs. 1.39 (I^2=75%) p=0.56	1.10 (I^2=22%) vs. 1.94 (I^2=80%) p=0.07
Total cholesterol (MD)	-7.61 (I^2=89%) vs. -12.71 (I^2=85%) p=0.55	**-24.33 (1 study) vs. -7.17 (I^2=91%) p=0.0008**	-14.17 (I^2=90%) vs. -7.79 (I^2=87%) p=0.58	-10.62 (I^2=95%) vs. -8.17 (I^2=85%) p=0.80
LDL cholesterol (MD)	-11.94 (I^2=91%) vs. -12.21 (I^2=91%) p=0.98	**-24.7 (1 study) vs. -9.22 (I^2=85%) p=0.03**	-11.67 (I^2=95%) vs. -12.18 (I^2=86%) p=0.97	-19.72 (I^2=73%) vs. -8.32 (I^2=89%) p=0.28
Cholesterol performance measure (OR)	1.31 (I^2=79%) vs. 1.85 (I^2=82%) p=0.29	2.6 (I^2=91%) vs. 1.28 (I^2=73%) p=0.12	2.12 (I^2=92%) vs. 1.37 (I^2=79%) p=0.53	1.51 (I^2=91%) vs. 1.60 (I^2=74%) p=0.89
Congestive heart failure studies				
Death (OR)	0.67 (I^2=59%) vs. 0.83 (I^2=0%) p=0.48	**0.64 (I^2=0%) vs. 1.18 (I^2=0%) p=0.02**	NA	0.72 (I^2=51%) vs. 0.67 (I^2=44%) p=0.82
Hospitalizations (OR)	0.77 (I^2=74%) vs. 0.91 (I^2=13%) p=0.55	0.87 (I^2=63%) vs. 0.66 (I^2=75%) p=0.61	NA	0.91 (I^2=47%) vs. 0.58 (1 study) p=0.07
CHF Hospitalizations (OR)	0.56 (I^2=38%) vs. 0.74 (I^2=0%) p=0.27	No studies in in-person group	NA	**0.75 (I^2=0%) vs. 0.47 (I^2=0%) p=0.04**
ACE/ARB performance measure (OR)	1.10 (I^2=0%) vs. 1.35 (1 study) p=0.51	1.2 (I^2=0%) vs. 1.03 (I^2=25%) p=0.61	NA	1.12 (I^2=0%) vs. 1.26 (I^2=0%) p=0.71

[a] If statistically significant main differences were found, the results are presented in bold type.

[b] If statistically significant subgroup differences were found, the group showing the larger effect is identified.

Abbreviations: ACE/ARB=angiotensin-converting enzyme inhibitor/angiotensin receptor blocking; CHF=congestive heart failure; LDL=low-density lipoprotein; MD=mean difference; OR=odds ratio

APPENDIX H. GLOSSARY

Abstract screening

The stage in a systematic review during which titles and abstracts of articles identified in the literature search are screened for inclusion or exclusion based on established criteria. Articles that pass the abstract screening stage are promoted to the full-text review stage.

ClinicalTrials.gov

A registry and results database of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov provides information about a trial's purpose, location, and participant characteristics among other details.

Cochrane Database of Systematic Reviews

A bibliographic database of peer-reviewed systematic reviews and protocols prepared by the Cochrane Review Groups in The Cochrane Collaboration.

Companion article

A publication from a trial that is not the article containing the main results of that trial. It may be a methods paper, a report of subgroup analyses, a report of combined analyses, or other auxiliary topic that adds information to the interpretation of the main publication.

Confidence interval (CI)

The range in which a particular result (such as a laboratory test) is likely to occur for everyone who has a disease. "Likely" usually means 95 percent of the time. Clinical research studies are conducted on only a certain number of people with a disease rather than all the people who have the disease. The study's results are true for the people who were in the study but not necessarily for everyone who has the disease. The CI is a statistical estimate of how much the study findings would vary if other different people participated in the study. A CI is defined by two numbers, one lower than the result found in the study and the other higher than the study's result. The size of the CI is the difference between these two numbers.

Data abstraction

The stage of a systematic review that involves a pair of trained researchers extracting reported findings specific to the research questions from the full-text articles that met the established inclusion criteria. These data form the basis of the evidence synthesis.

DistillerSR

An online application designed specifically for the screening and data extraction phases of a systematic review.

Embase

The Excerpta Medica database (EMBASE) produced by Elsevier, a major biomedical and pharmaceutical database indexing over 3500 international journals in the following fields: drug research, pharmacology, pharmaceutics, toxicology, clinical and experimental human medicine, health policy and management, public health, occupational health, environmental health, drug dependence and abuse, psychiatry, forensic medicine, and biomedical engineering or instrumentation. There is selective coverage for nursing, dentistry, veterinary medicine, psychology, and alternative medicine.

Exclusion criteria

The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions.

Full-text review

The stage of a systematic review in which a pair of trained researchers evaluates the full-text of study articles for potential inclusion in the review.

GRADE

Grading of Recommendations Assessment, Development, and Evaluation (GRADE), a system of assessing the quality of medical evidence and evaluating the strength of recommendations based on the evidence.

Inclusion criteria

The criteria, or standards, set out before the systematic review. Inclusion criteria are used to determine whether an individual study can be included in a systematic review. Inclusion criteria may include population, study design, sex, age, type of disease being treated, previous treatments, and other medical conditions.

Optimal information size

The number of patients that need to be included in a pooled analysis (meta-analysis) to provide sufficient power to detect the smallest clinically important difference in treatment effect.

PRISMA

Preferred Reporting Items for Systematic Reviews and Meta-Analyses, an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

Publication bias

The tendency of researchers to publish experimental findings that have a positive result, while not publishing the findings when the results are negative or inconclusive. The effect of publication bias is that published studies may be misleading. When information that differs from that of the published study is not known, people are able to draw conclusions using only information from the published studies.

PubMed®

A database of citations for biomedical literature from MEDLINE®, life science journals, and online books in the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and preclinical sciences.

Randomized controlled trial (RCT)

A prospective, analytical, experimental study using primary data generated in the clinical environment. Individuals similar at the beginning of the trial are randomly allocated to two or more treatment groups and the outcomes the groups are compared after sufficient followup time. Properly executed, the RCT is the strongest evidence of the clinical efficacy of preventive and therapeutic procedures in the clinical setting.

Risk

A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Statistical significance

A mathematical technique to measure whether the results of a study are likely to be true. Statistical significance is calculated as the probability that an effect observed in a research study is occurring because of chance. Statistical significance is usually expressed as a P-value. The smaller the P-value, the less likely it is that the results are due to chance (and more likely that the results are true). Researchers generally believe the results are probably true if the statistical significance is a P-value less than 0.05 (p<.05).

Strength of evidence (SOE)

A measure of how confident reviewers are about decisions that may be made based on a body of evidence. SOE is evaluated using one of four grades: (1) *High* confidence that the evidence reflects the true effect; further research is very unlikely to change reviewer confidence in the estimate of effect; (2) *moderate* confidence that the evidence reflects the true effect; further research may change the confidence in the estimate of effect and may change the estimate; (3) *low* confidence that the evidence reflects the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; and (4) *insufficient*; the evidence either is unavailable or does not permit a conclusion.

Systematic review

A summary of the clinical literature. A systematic review is a critical assessment and evaluation of all research studies that address a particular clinical issue. The researchers use an organized method of locating, assembling, and evaluating a body of literature on a particular topic using a set of specific criteria. A systematic review typically includes a description of the findings of the collection of research studies. The systematic review may also include a quantitative pooling of data, called a meta-analysis.

"Effects of Nurse-Managed Protocols in the Outpatient Management of Adults with Chronic Conditions: A Systematic Review and Meta-analysis"

Reanalysis of CVD-related Data

Prepared by Jennifer McDuffie, Andrzej Kosinski, Ryan Shaw, John Williams

Our report, "Effects of Nurse-Managed Protocols in the Outpatient Management of Adults with Chronic Conditions: A Systematic Review and Meta-analysis," was submitted to the Annals of Internal Medicine for publication.

After this report was completed and published, the statistical reviewer for a journal submission requested that we reanalyze the data using a statistical approach that accounted for small numbers of studies.

In response to this recommendation, we reanalyzed the data using the Knapp and Hartung (2003) method to adjust the standard errors of the estimated coefficients to help to account for the uncertainty in the estimate of the amount of (residual) heterogeneity. As expected, this analyses did not change any of the point estimates , but 95% confidence intervals increased for some of the outcomes. The original summary estimates of effect and the revised estimates of effect are summarized in the table below.

Table of original vs. revised Confidence Intervals

Statistic (direction of comparison: RNP vs. UC)	Original summary estimates (95% CI)	Revised summary estimates (95% CI_
Mean difference in HbA1c	-0.40 (-0.63 to -0.17)	-0.40 (-0.70 to -0.10)
(non-RCTs)	-1.12 (-2.99 to 0.74)	
Mean difference in SBP	-3.68 (-5.67 to -1.69)	-3.68 (-6.31 to -1.05)
Mean difference in DBP	-1.56 (-2.57 to -0.55)	-1.56 (-2.76 to -0.36)
Achieve target BP values vs. controls (OR)	1.41 (1.21 to 1.78)	1.41 (0.98 to 2.02)
Mean difference in total cholesterol (mmol/L)	-0.24 (-0.46 to 0.02)	-0.24 (-0.54 to 0.05)
Mean difference in low-density-lipoprotein cholesterol	-0.31 (-0.62 to 0.00)	-0.31 (-0.73 to 0.11)
Achieve target TC values vs. controls (OR)	1.54 (1.14 to 2.08)	1.54 (1.02 to 2.31)

OR = Odds ratio

Reference: Knapp, G. & Hartung, J. (2003). Improved tests for a random effects meta-regression with a single covariate. Statistics in Medicine, 22, 2693–2710.