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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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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

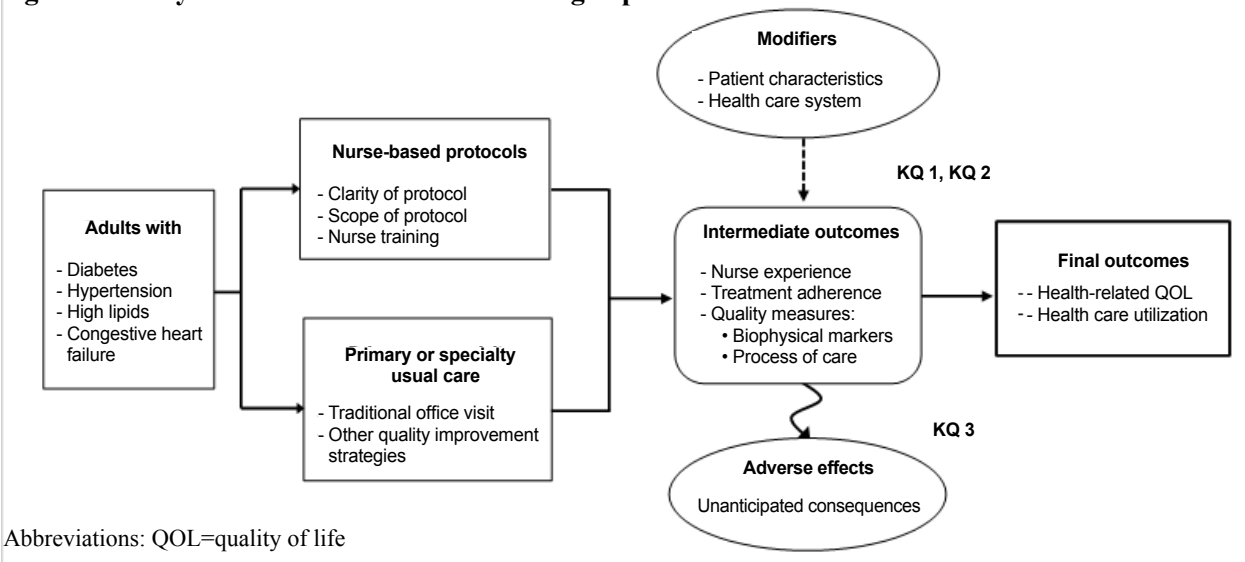
KQ 2. In studies of nurse-managed protocols, how well do participating nurses adhere to the protocol?

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

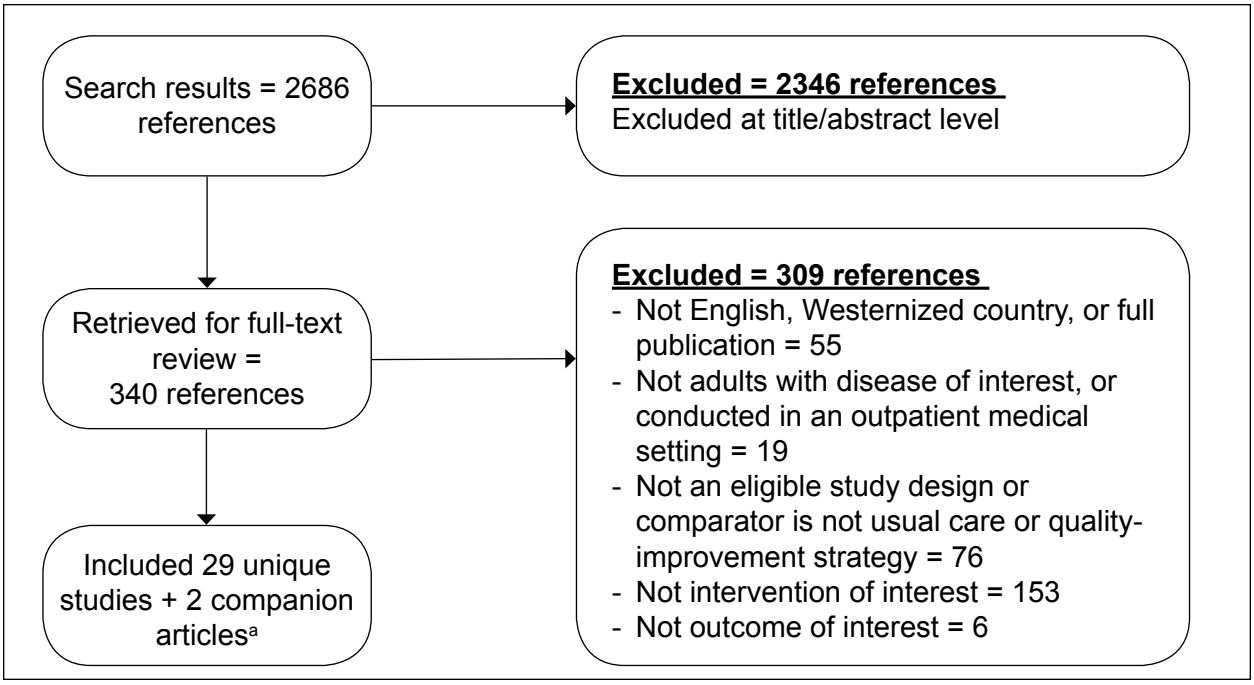
A draft version of the report was reviewed by technical experts and clinical leadership. A transcript of their comments can be found in Appendix E, which elucidates how each comment was considered in the final report.

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



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

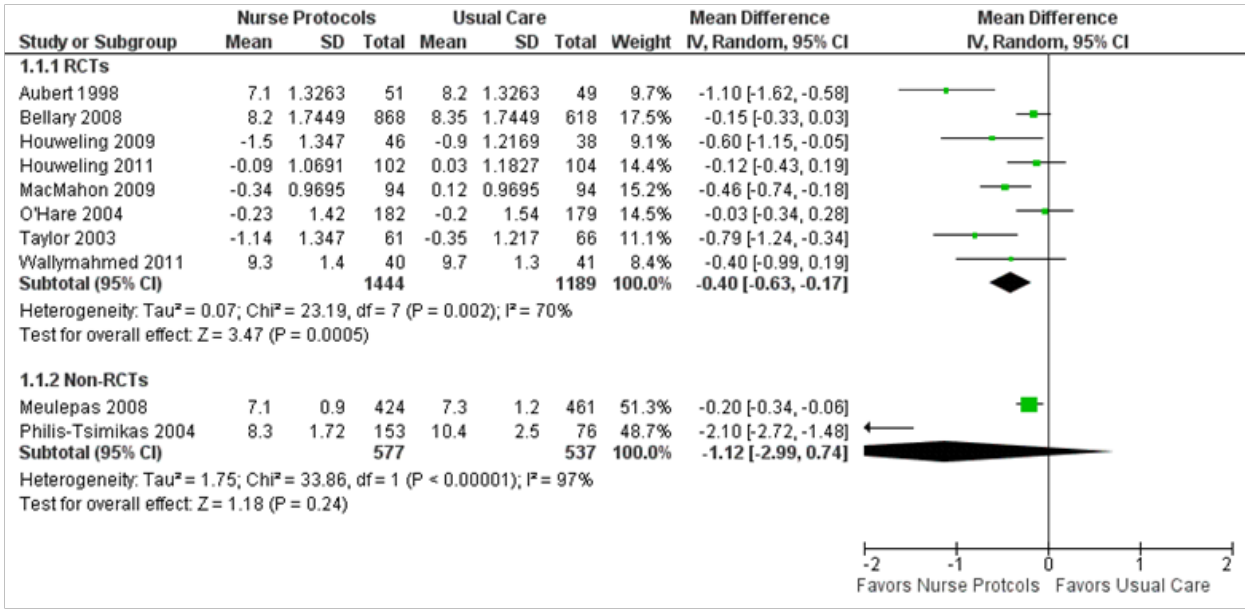
Biophysical Markers

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

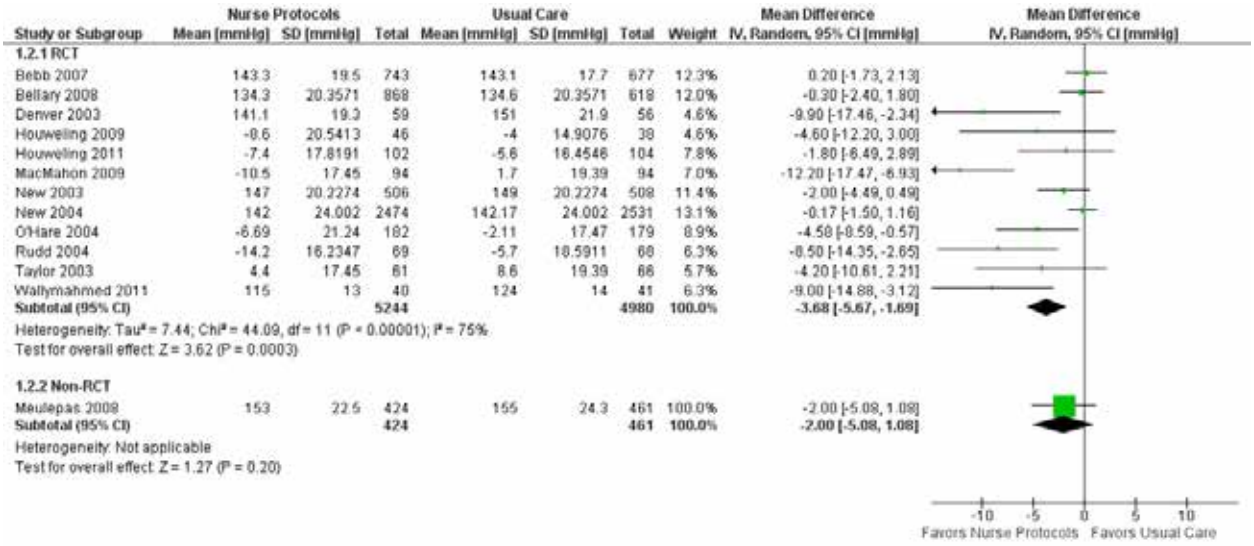
Systolic and diastolic blood pressure (SBP, DBP). Of the 18 studies conducted in patients with elevated cardiovascular risk, 14 targeted blood pressure control. Twelve RCTs (10,224 patients) and one non-RCT (885 patients) were included in the quantitative analyses. Compared with usual care, nurse-managed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

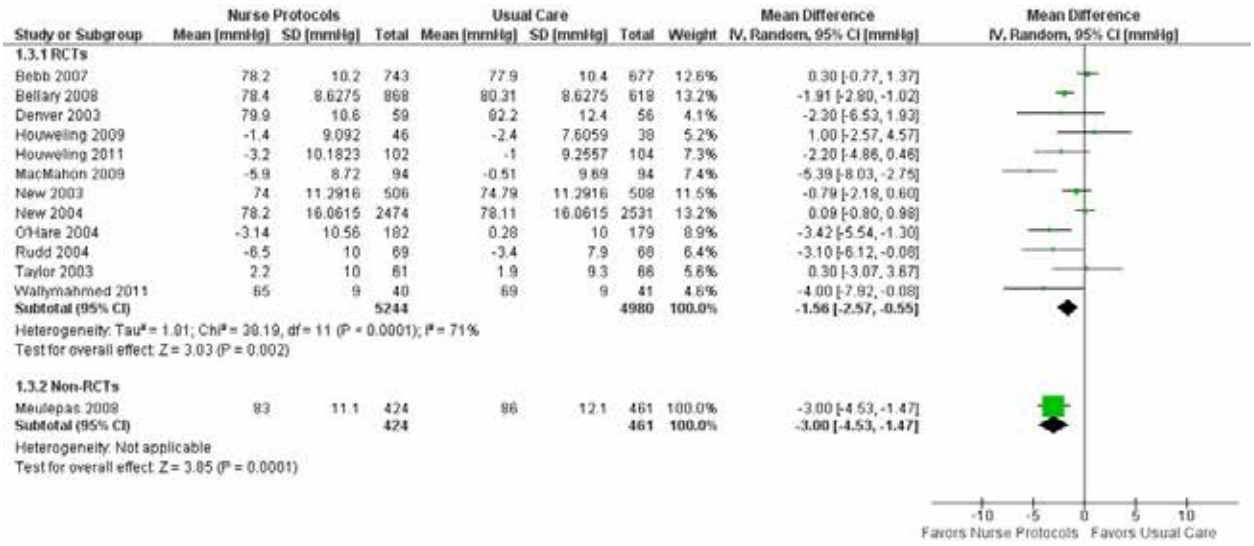
We performed subgroup analyses to explore for differences in intervention effects between studies conducted in the United States versus other countries, studies targeting BP alone versus multiple conditions, studies incorporating self-management plans or specific behavioral interventions versus those 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

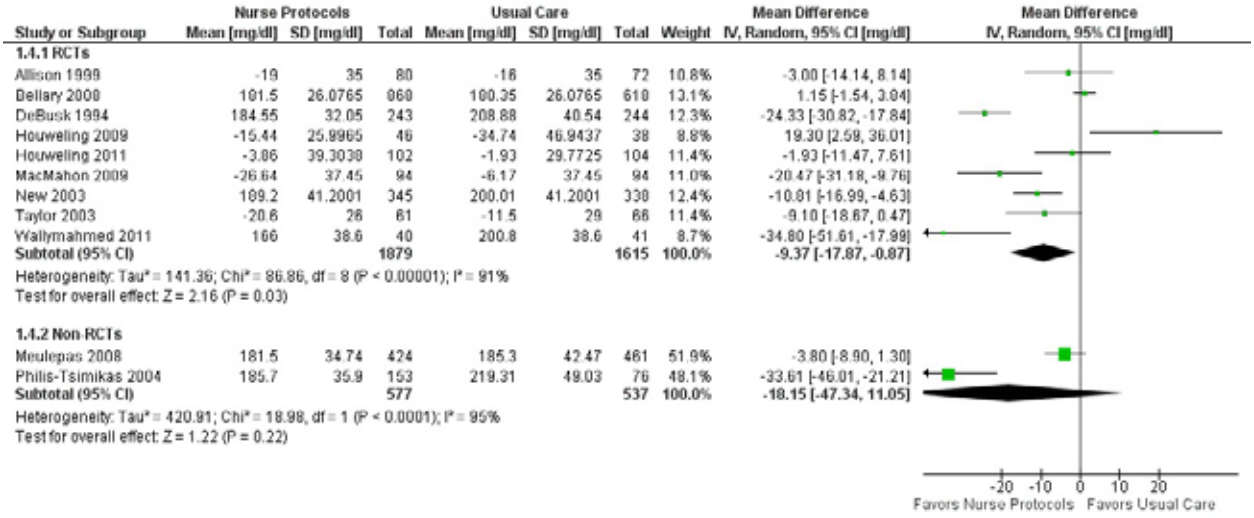
Total cholesterol and low-density lipoprotein (LDL) cholesterol. Of the 18 studies conducted in patients with elevated cardiovascular risk, 14 targeted hyperlipidemia. Nine RCTs (3494 patients) and two non-RCTs (1114 patients) were included in the quantitative analyses. Compared with usual care, nurse-managed 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).

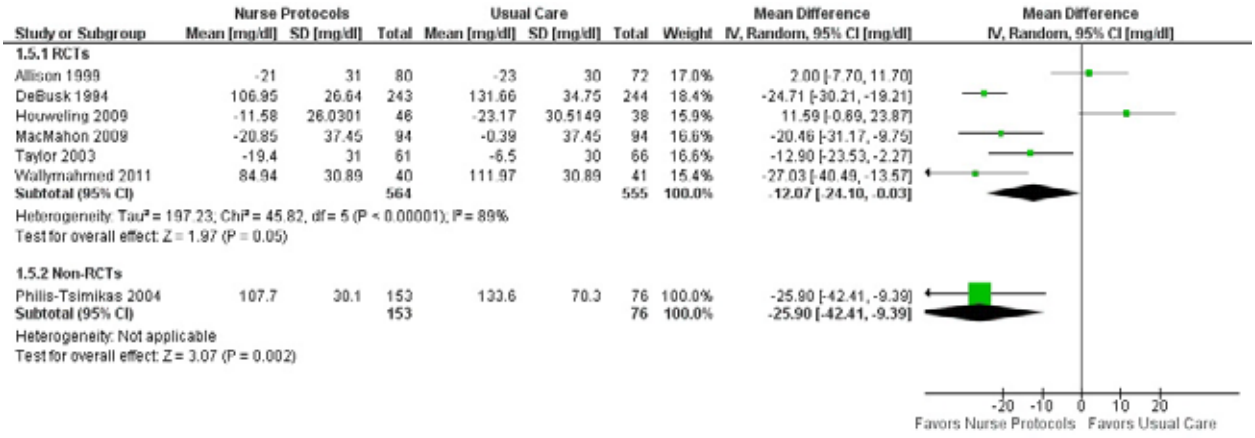
Effects of nurse-managed protocols on total cholesterol and LDL cholesterol from the two non-RCTs[67,71] were in the same direction, with nonstatistically significant reductions in total cholesterol. However, there was a statistically significant reduction (MD -25.90; 95% CI, -42.41 to -9.39) in LDL 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

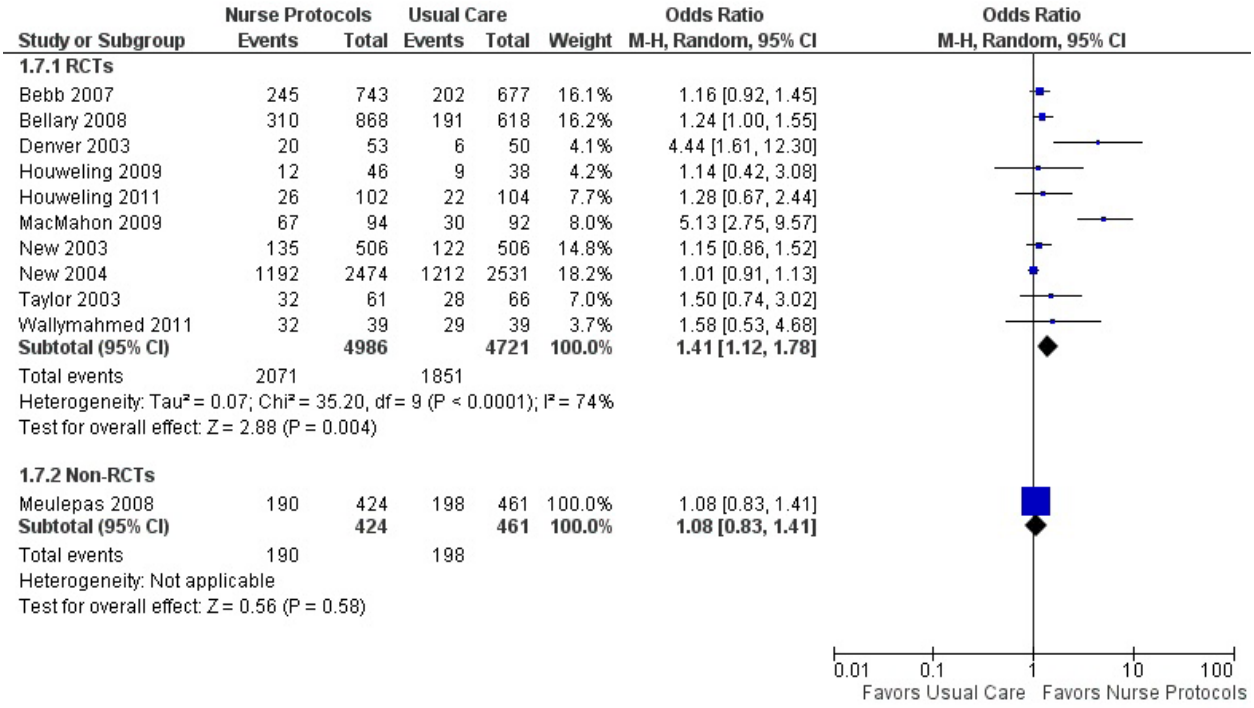
Target blood pressure values. Of the 18 studies conducted in patients with elevated cardiovascular risk, 11 focused on achieving target blood pressure values. Figure 8 shows the forest plot of the random-effects meta-analysis of nurse-managed protocols on the process measure of achieving target total 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



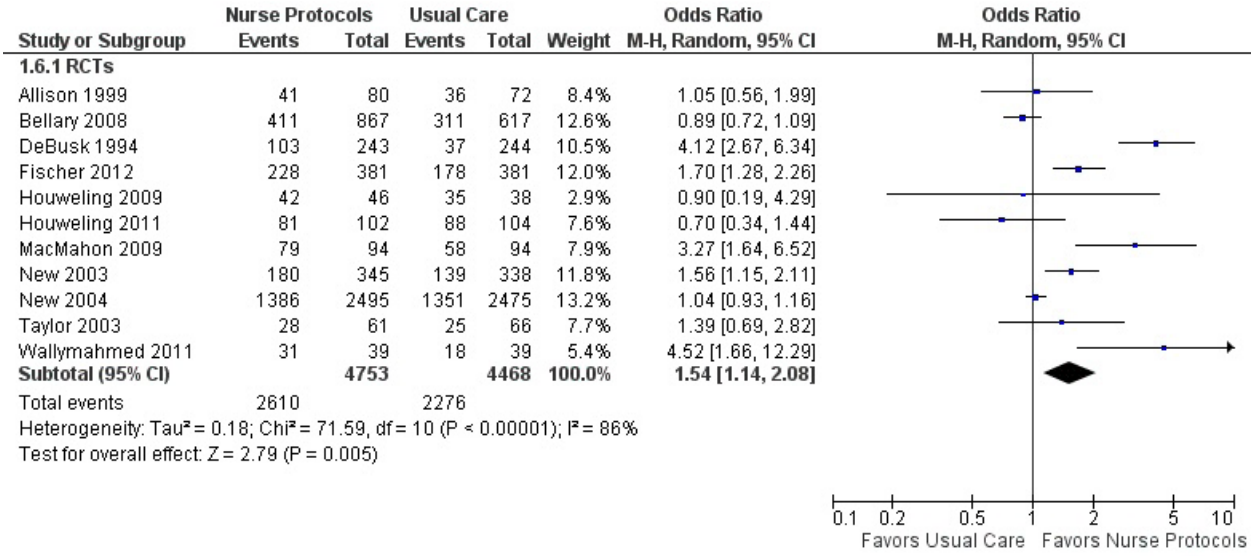
Abbreviations: CI=confidence interval; RCT=randomized controlled trial

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



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

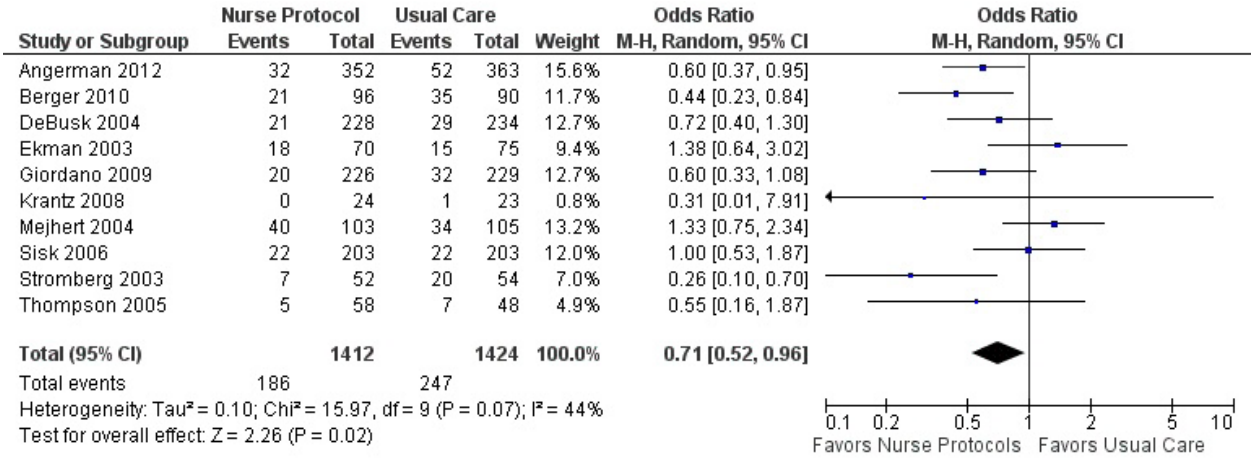
Biophysical Markers

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



Abbreviations: CI=confidence interval

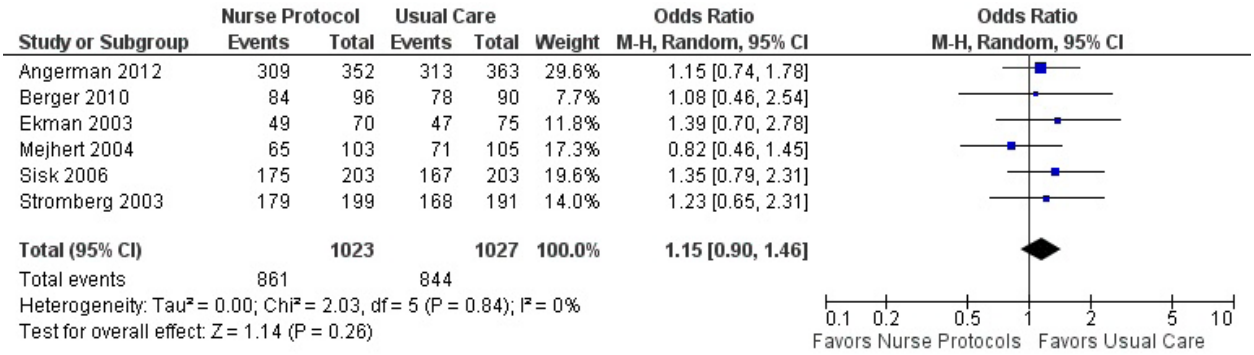
Health-related quality of life (HRQOL). Four studies reported effects on general measures of HRQOL.[50,66,73,75] Two of these found significant effects on the SF-36 physical health component: Angermann et al.,[50] MD 2.1 (95% CI, 0.2 to 4.0), and Sisk et al.,[73] MD 3.1 (95% CI, 0.7 to 5.5). In a small 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

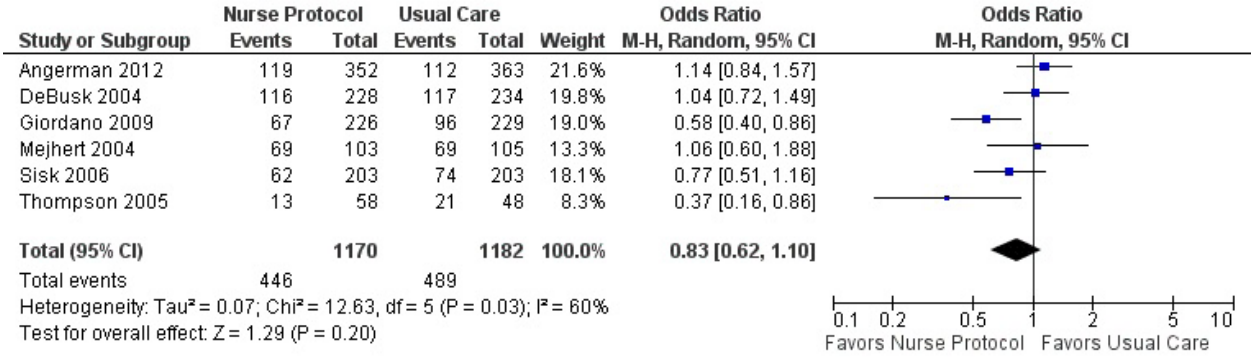
Hospitalizations

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).

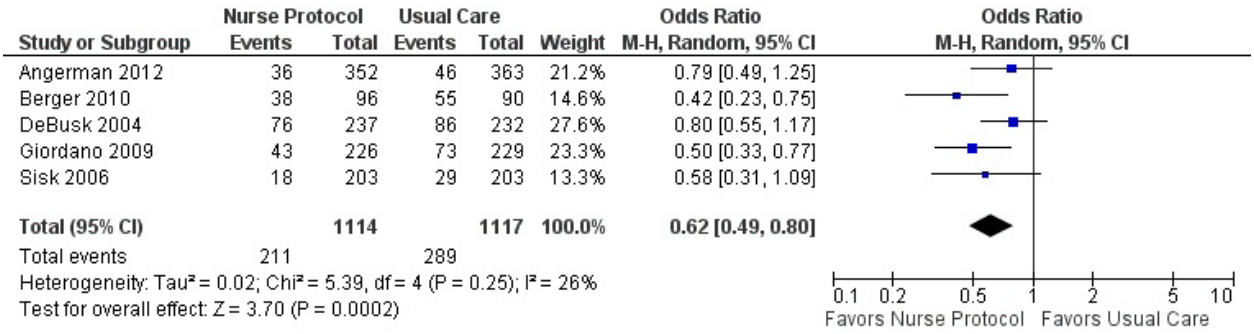
Figure 12. Effects of nurse-managed protocols on total hospitalizations



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



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	Strength of Evidence Domains				Effect Estimate (95% CI)	SOE
	Number of Studies (Patients)	Study Design/ Risk of Bias	Consistency Directness	Precision Publication Bias		
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 ≥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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Addendum to "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

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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 (non-RCTs)	-0.40 (-0.63 to -0.17) -1.12 (-2.99 to 0.74)	-0.40 (-0.70 to -0.10)
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.