Annals of Internal Medicine | Review

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

## A Systematic Review and Meta-analysis

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**Background:** Changes in federal health policy are providing more access to medical care for persons with chronic disease. Providing quality care may require a team approach, which the American College of Physicians calls the "medical home." One new model may involve nurse-managed protocols.

**Purpose:** To determine whether nurse-managed protocols are effective for outpatient management of adults with diabetes, hypertension, and hyperlipidemia.

**Data Sources:** MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and CINAHL from January 1980 through January 2014.

**Study Selection:** Two reviewers used eligibility criteria to assess all titles, abstracts, and full texts and resolved disagreements by discussion or by consulting a third reviewer.

**Data Extraction:** One reviewer did data abstractions and quality assessments, which were confirmed by a second reviewer.

**Data Synthesis:** From 2954 studies, 18 were included. All studies used a registered nurse or equivalent who titrated medications by following a protocol. In a meta-analysis, hemoglobin $A_{1c}$ level decreased by 0.4% (95% CI, 0.1% to 0.7%) ($n = 8$); systolic and diastolic blood pressure decreased by 3.68 mm Hg (CI, 1.05 to 6.31 mm Hg) and 1.56 mm Hg (CI, 0.36 to 2.76 mm Hg), respectively ($n = 12$); total cholesterol level decreased by 0.24 mmol/L (9.37 mg/dL) (CI, 0.54-mmol/L decrease to 0.05-mmol/L increase [20.77-mg/dL decrease to 2.02-mg/dL increase]) ($n = 9$); and low-density-lipoprotein cholesterol level decreased by 0.31 mmol/L (12.07 mg/dL) (CI, 0.73-mmol/L decrease to 0.11-mmol/L increase [28.27-mg/dL decrease to 4.13-mg/dL increase]) ($n = 6$).

**Limitation:** Studies had limited descriptions of the interventions and protocols used.

**Conclusion:** A team approach that uses nurse-managed protocols may have positive effects on the outpatient management of adults with chronic conditions, such as diabetes, hypertension, and hyperlipidemia.

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Medical management of chronic illness consumes 75% of every health care dollar spent in the United States (1). Thus, provision of economical and accessible—yet high-quality—care is a major concern. Diabetes mellitus, hypertension, and hyperlipidemia are prime examples of chronic diseases that cause substantial morbidity and mortality (2, 3) and require long-term medical management. For each of these disorders, most care occurs in outpatient settings where well-established clinical practice guidelines are available (4–7). Despite the availability of these guidelines, there are important gaps between the care recommended and the care delivered (8–10). The shortage of primary care clinicians has been identified as 1 barrier to the provision of comprehensive care for chronic disease (11, 12) and is an impetus to develop strategies for expanding the roles and responsibilities of other interdisciplinary team members to help meet this increasing need.

The patient-centered medical home concept was developed in an effort to serve more persons and improve chronic disease care. It is a model of primary care transformation that builds on other efforts, such as the chronic care model (13), and includes the following elements: patient-centered orientation toward the whole person, team-based care coordinated across the health care system and community, enhanced access to care, and a systems-based approach to quality and safety. Care teams may include nurses, primary care providers, pharmacists, and behavioral health specialists. An organizing principle for care teams is to utilize personnel at the highest level of their skill set, which is particularly relevant given the expected increase in demand for primary care services resulting from the Patient Protection and Affordable Care Act.

With this increased demand, the largest health care workforce, registered nurses (RNs), may be a valuable asset alongside other nonphysician clinicians, including physician assistants, nurse practitioners, and clinical pharmacists, to serve more persons and improve chronic disease care. Robust evidence supports the effectiveness of nurses in providing patient education about chronic disease and secondary prevention strategies (14–19). With clearly defined protocols and training, nurses may also be able to order relevant diagnostic tests, adjust routine medications, and appropriately refer patients.

Our purpose was to synthesize the current literature describing the effects of nurse-managed protocols, includ-

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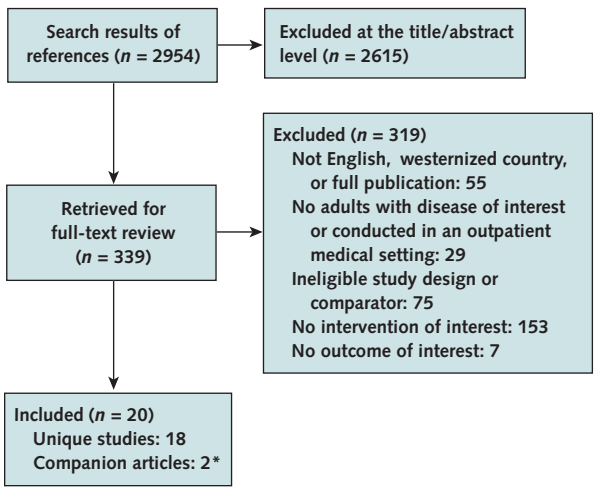
*Figure 1.* **Summary of evidence search and selection.**




* Methods or follow-up articles.

ing medication adjustment, for the outpatient management of adults with common chronic conditions, namely diabetes, hypertension, and hyperlipidemia.

## METHODS

We followed a standard protocol for all steps of this review. A technical report that fully details our methods and presents results for all original research questions is available at www.hsrd.research.va.gov/publications/esp/reports.cfm.

### Data Sources and Searches

In consultation with a master librarian, we searched MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials, EMBASE, and CINAHL from 1 January 1980 through 31 January 2014 for English-language, peer-reviewed publications evaluating interventions that compared nurse-managed protocols with usual care in studies targeting adults with chronic conditions (**Supplement 1**, available at www.annals.org).

We selected exemplary articles and used a Medical Subject Heading analyzer to identify terms for "nurse protocols." We added selected free-text terms and validated search terms for randomized, controlled trials (RCTs) and quasi-experimental studies, and we searched bibliographies of exemplary studies and applicable systematic reviews for missed publications (15, 17, 20–29). To assess for publication bias, we searched ClinicalTrials.gov to identify completed but unpublished studies meeting our eligibility criteria.

### Study Selection, Data Extraction, and Quality Assessment

Two reviewers used prespecified eligibility criteria to assess all titles and abstracts (**Supplement 2**, available at www.annals.org). Eligibility criteria included the involvement of an RN or a licensed practical nurse (LPN) functioning beyond the usual scope of practice, such as adjusting medications and conducting interventions based on a written protocol. Potentially eligible articles were retrieved for further evaluation. Disagreements on inclusion or exclusion were resolved by discussion or a third reviewer. Studies excluded at full-text review are listed in **Supplement 3** (available at www.annals.org). Abstraction and quality assessment were done by 1 reviewer and confirmed by a second. We piloted the abstraction forms, designed specifically for this review, on a sample of included articles. Key characteristics abstracted included patient descriptors, setting, features of the intervention and comparator, match between the sample and target populations, extent of the nurse interventionist's training, outcomes, and quality elements. **Supplements 4** and **5** (available at www.annals.org) summarize quality criteria and ratings, respectively.

Because many studies were done outside the United States, we queried the authors of such studies about the education and scope of practice of the nurse interventionists. Authors were e-mailed a table detailing the credentialing and scope of practice of various U.S. nurses and asked to classify their nurse interventionist.

### Data Synthesis and Analysis

The primary outcomes were the effects of nurse-managed protocols on biophysical markers (for example, glycosylated hemoglobin or hemoglobin $A_{1c}$ [$HbA_{1c}$]), patient treatment adherence, nurse protocol adherence, adverse effects, and resource use. When quantitative synthesis (that is, meta-analysis) was feasible, dichotomous outcomes were combined using odds ratios and continuous outcomes were combined using mean differences in random-effects models. For studies with unique but conceptually similar outcomes, such as ordering a guideline-indicated laboratory test, we synthesized outcomes across conditions if intervention effects were sufficiently homogeneous. We used the Knapp and Hartung method (30, 31) to adjust the SEs of the estimated coefficients.

For categories with several potential outcomes (for example, biophysical markers) that may vary across chronic conditions, we selected outcomes for each chronic condition a priori: $HbA_{1c}$ level for diabetes, blood pressure (BP) for hypertension, and cholesterol level for hyperlipidemia. In 1 example (32), we imputed missing SDs using estimates from similar studies.

We computed summary estimates of effect and evaluated statistical heterogeneity using the Cochran $Q$ and $I^2$ statistics. We did subgroup analyses to examine potential sources of heterogeneity, including where the study was conducted and intervention content. Subgroup analyses involved indirect comparisons and were subject to confounding; thus, results were interpreted cautiously. Publication bias was assessed using a ClinicalTrials.gov search and fun-

nel plots when at least 10 studies were included in the analysis.

When quantitative synthesis was not feasible, we analyzed data qualitatively. We gave more weight to evidence from higher-quality studies with more precise estimates of effect. The qualitative syntheses identified and documented patterns in efficacy and safety of the intervention across conditions and outcome categories. We analyzed potential reasons for inconsistency in treatment effects across studies by evaluating variables, such as differences in study population, intervention, comparator, and outcome definitions.

We followed the approach recommended by the Agency for Healthcare Research and Quality (33) to evaluate the overall strength of the body of evidence. This approach assesses the following 4 domains: risk of bias, consistency, directness, and precision. These domains were considered qualitatively, and a summary rating of high, moderate, low, or insufficient evidence was assigned.

### Role of the Funding Source

The Veterans Affairs Quality Enhancement Research Initiative funded the research but did not participate in the conduct of the study or the decision to submit the manuscript for publication.

## RESULTS

Our electronic and manual searches identified 2954 unique citations (**Figure 1**). Of the 23 potentially eligible studies, 4 were excluded because we could not verify whether nurses had the authority to initiate or titrate medications and the author did not respond to our query for clarification (34–37). We excluded a trial of older adults in which we could not differentiate the target illnesses (38). Approximately two thirds of the authors we contacted for missing data or clarification responded.

We included 18 unique studies (23 004 patients) that focused on patients with elevated cardiovascular risk (**Table**) (32, 39–55). Of these, 16 were RCTs and 2 were controlled before-and-after studies on diabetes (49, 53). The comparator was usual care in all but 1 study, in which a reverse-control design was used, and each intervention served as the control for the other. Eleven studies were done in Western Europe and 7 in the United States. Median age of participants was 58.3 years (range, 37.2 to 72.1 years) based on 16 studies. Approximately 47% of the participants were female. Race was not reported in 84% of the studies. **Supplement 5** gives detailed study characteristics. No outstanding studies were identified through ClinicalTrials.gov. **Supplement 6** provides funnel plots that assess publication bias (available at www.annals.org).

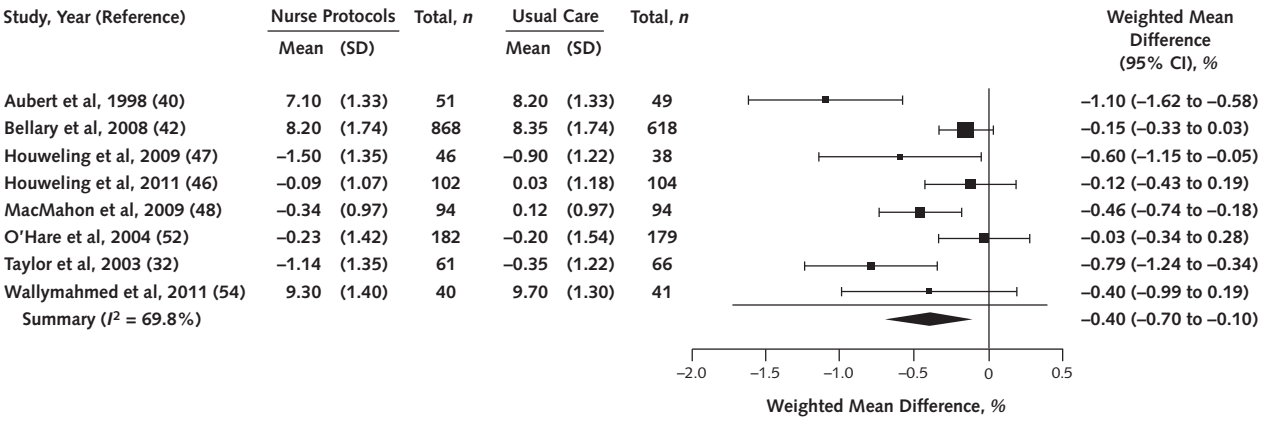
Overall, these studies displayed moderate risk of bias. Two studies were judged as having a high risk of bias because of inadequate randomization (44, 53), 12 were moderate risk (32, 39–41, 43, 47–52, 54), and 4 were low risk (42, 45, 46, 55). Other design issues affecting risk-of-bias ratings were possible contamination from a concurrent

***Table.*** **Study and Patient Characteristics of Included Diabetes, Hypertension, and Hyperlipidemia Studies**

| Characteristic | Cardiovascular Risk Studies, *n (%)* |
|---|---|
| **Total** | |
| Studies | 18 |
| Patients* | 23 004 |
| **Design** | |
| RCT | 16 (89) |
| Non-RCT | 2 (11) |
| **Location** | |
| United States | 7 (39) |
| Western Europe | 11 (61) |
| **Setting** | |
| General medical hospital | 12 (67) |
| Specialty hospital | 3 (17) |
| Primary clinic and specialty hospital | 2 (11) |
| Telephone- and clinic-delivered care | 1 (5.5) |
| **Intervention** | |
| Target | |
| Glucose | 15 (83) |
| Blood pressure | 11 (61) |
| Lipids | 9 (50) |
| Delivery | |
| Clinic visits | 15 (83) |
| Primarily telephone | 3 (17) |
| Duration | |
| 6 mo | 2 (11) |
| 12 mo | 8 (44.5) |
| >12 mo† | 8 (44.5) |
| **Nurse training** | |
| Specialist‡ | 3 (17) |
| Received study-specific training | 10 (55) |
| Case manager | 1 (5.5) |
| Not described | 4 (22) |
| **Medication initiation** | 11 (61) |
| **Education or behavioral strategy** | |
| Education | 16 (89) |
| Specific behavioral strategy§ | 3 (17) |
| Self-management plan | 9 (50) |
| **Outcome** | |
| Hemoglobin $A_{1c}$ level | 12 (67) |
| Blood pressure | 14 (78) |
| Cholesterol level | 15 (83) |
| Performance measure | 13 (72) |
| Behavioral adherence | 4 (22) |
| Protocol adherence | 1 (6) |
| **Risk of bias/quality** | |
| Low/good | 4 (22) |
| Moderate/fair | 12 (67) |
| High/poor | 2 (11) |

RCT = randomized, controlled trial.
* Number of patients represents the total mean of 22 839 and 23 170 because in 1 included study (50), hypertension and hyperlipidemia results were reported on 2 different but overlapping populations due to randomization.
† Range, 14–36 mo.
‡ Clinical certification or diabetes nurse educator.
§ Motivational interviewing.

*Figure 2.* **Effects of nurse-managed protocols on hemoglobin $A_{1c}$ level.**




intervention, unblinded outcome assessors, and incomplete outcomes data.

### Characteristics of the Interventions

All 18 study interventions used a protocol and required the nurse to titrate medications; however, only 11 reported that the nurse was independently allowed to initiate new medications. All but 1 study (55) provided the actual algorithm or citation. An RN (not an advanced practice RN) was the interventionist in all U.S. studies; a nurse with an equal scope of practice was the interventionist in the non-U.S. studies. No studies reported use of LPNs. In 14 studies, interventions were delivered in a nurse-led clinic (39–42, 44, 46–54). Supervisors were nearly always physicians. Of the studies reporting nurses' training, 3 used specialists (for example, diabetes-certified), 10 used RNs with study-specific training, and 1 used nurse case managers with experience in coordinating long-term care.

Nurse protocols included additional components, such as education or self-management, in 16 studies. Two studies (41, 47) did not report additional intervention. Baseline characteristics showed that patients with diabetes had an elevated $HbA_{1c}$ level of approximately 8.0% or greater. Most patients with hypertension had moderate hypertension, and patients with hyperlipidemia had borderline high lipid levels. Outcomes were assessed at 6 to 36 months, with most studies reporting outcomes at 12 months or longer.

### Diabetes Outcomes

Of the 15 studies done in patients with diabetes, 10 RCTs (2633 patients) targeted glucose control. **Figure 2** shows the forest plot of the random-effects meta-analysis on $HbA_{1c}$ level. Compared with usual care, nurse-managed protocols decreased $HbA_{1c}$ levels by 0.4% (95% CI, 0.1% to 0.7%) ($n = 8$) and effects varied substantially ($Q = 23.19$; $I^2 = 70\%$). In the 2 non-RCTs (49, 53) not included in **Figure 2**, effects of the protocols on $HbA_{1c}$ level were larger and in the same direction but had higher variability. Thus, nurse-managed protocols were associated with a highly variable mean decrease in $HbA_{1c}$ level.

Other diabetes-related performance measures were rarely reported (**Supplement 6**). In 1 controlled before-and-after study (53), achieving target eye examination, urinary microalbumin–creatinine ratio, and foot examination goals was reported to reach 80% to 100% using nurse-managed protocols. A second study (49) found a nonsignificant increase in intervention patients achieving eye and foot examination goals compared with control participants. Reduction in the proportion of patients with an $HbA_{1c}$ level of 8.5% or greater was achieved in 1 study (odds ratio, 1.69 [CI, 1.25 to 2.29]) (49).

### BP Outcomes

Fourteen studies reported BP outcomes: 13 RCTs (10 362 patients) and 1 non-RCT (885 patients). Restricted to the 12 RCTs specifically addressing BP (10 224 patients), the intervention decreased systolic BP by 3.68 mm Hg (CI, 1.05 to −6.31 mm Hg) and diastolic BP by 1.56 mm Hg (CI, 0.36 to 2.76 mm Hg), with high variability ($I^2 > 70\%$) (**Figures 3** and **4**). Funnel plots suggested possible publication bias with systolic but not diastolic BP (**Supplement 6**). Overall, nurse-managed protocols were associated with a mean decrease in systolic and diastolic BP.

Eleven of the 18 studies focused on achieving various target BPs: 10 RCTs (9707 patients) and 1 non-RCT (885 patients). When the analysis was restricted to RCTs, nurse-managed protocols were more likely to achieve target BP than control protocols (odds ratio, 1.41 [CI, 0.98 to 2.02]), but these results could have been due to chance, and treatment effects were highly variable ($Q = 35.20$; $I^2 = 74\%$) (**Supplement 7**, available at www.annals.org). Using the summary odds ratio and median event rate from the control group of the trials that implemented nurse protocols, we estimated the absolute treatment effect as a risk

difference of 120 more patients achieving target total BP per 1000 patients (CI, 6 fewer to 244 more). Funnel plots suggested some asymmetry but no clear publication bias.

### Hyperlipidemia Outcomes

Fifteen studies reported hyperlipidemia outcomes: 13 RCTs (14 817 patients) and 2 non-RCTs (1114 patients). Of these, 9 RCTs (3494 patients) specifically addressed total cholesterol levels and 6 RCTs specifically addressed low-density lipoprotein levels (1095 patients). In analyses restricted to these trials, the intervention was associated with a decrease in total cholesterol level. Total cholesterol levels decreased by 0.24 mmol/L (9.37 mg/dL) (CI, 0.54-mmol/L decrease to 0.05-mmol/L increase [20.77-mg/dL decrease to 2.02-mg/dL increase]) ($n = 9$), and low-density lipoprotein cholesterol levels decreased by 0.31 mmol/L (12.07 mg/dL) (CI, 0.73-mmol/L decrease to 0.11-mmol/L increase [28.27-mg/dL decrease to 4.13-mg/dL increase]) ($n = 6$), with marked variability in intervention effects ($I^2 \geq 89\%$) (**Figure 4**). Effects of nurse-managed protocols on total and low-density lipoprotein cholesterol levels from the 2 non-RCTs (49, 53) were in the same direction. Reductions in total cholesterol level were not statistically significant. Overall, nurse-managed protocols were associated with a mean decrease in total and low-density lipoprotein cholesterol levels.

All 11 studies (9221 patients) targeting various total cholesterol levels were included in the quantitative analysis (**Supplement** 7). Nurse-managed protocols were statistically significantly more likely to achieve target total cholesterol levels than control protocols (odds ratio, 1.54 [CI,

*Figure 3.* **Effects of nurse-managed protocols on systolic (*top*) and diastolic (*bottom*) blood pressure.**

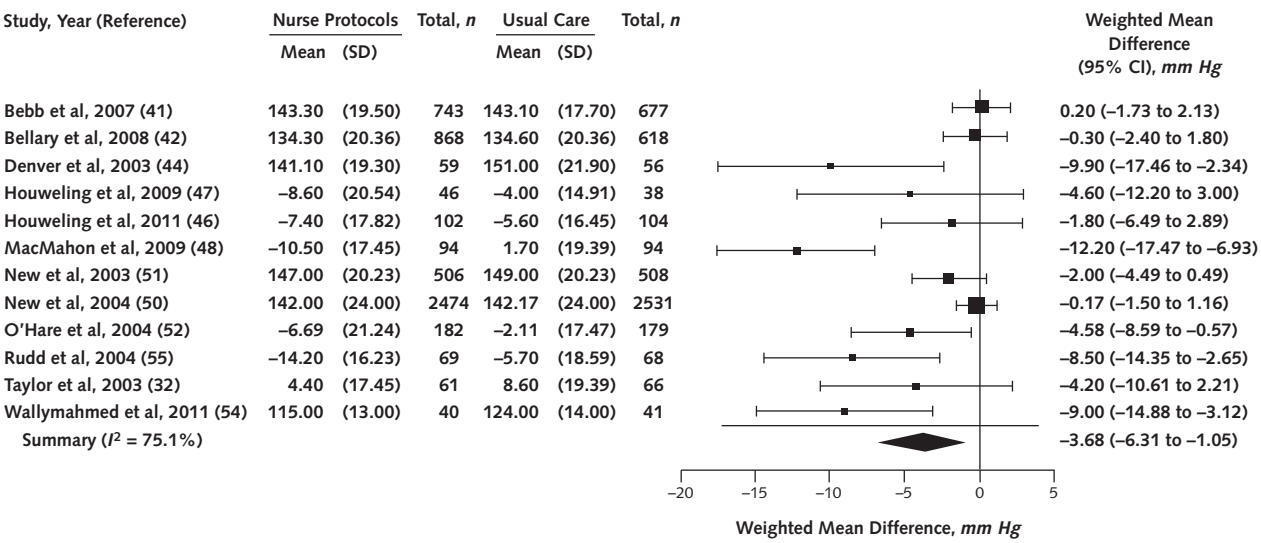
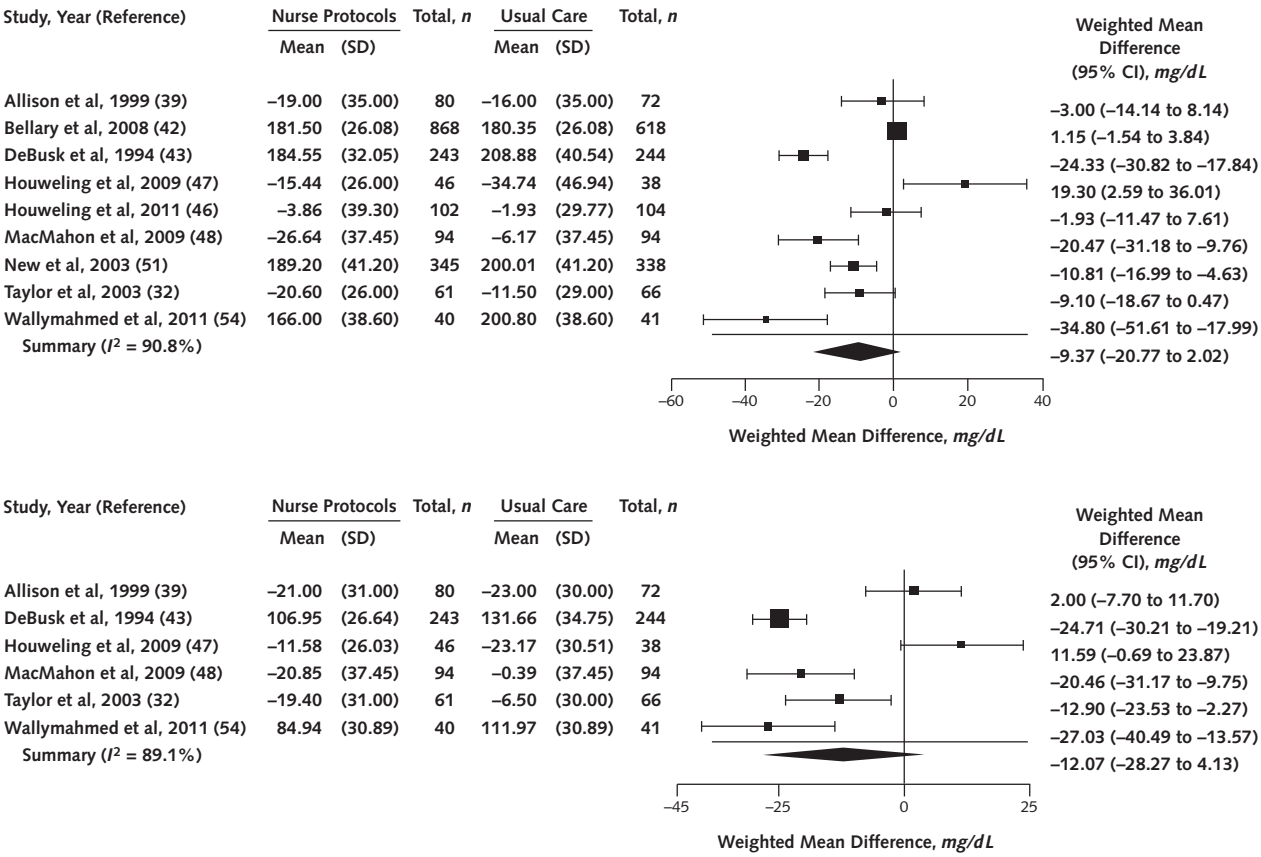


*Figure 4.* **Effects of nurse-managed protocols on total cholesterol (*top*) and low-density lipoprotein cholesterol (*bottom*) levels.**




To convert mg/dL to mmol/L, multiply by 0.0259.

1.02 to 2.31]), with substantial variability in treatment effects ($Q = 71.59$; $I^2 = 86\%$). Using the summary odds ratio and median event rate from the control group of the RCTs, we estimated the absolute treatment effect as a risk difference of 106 more patients achieving target total cholesterol levels per 1000 patients (CI, 5 to 196). Funnel plots did not suggest publication bias (**Supplement 6**).

### Patient Adherence to Treatment

Behavioral adherence was reported in 4 studies (39, 43, 48, 49). In 1 study, the rate of daily medication adherence (±SE) for the intervention group during the 6-month study was 80.5% ± 23.0% compared with 69.2% ± 31.1% for the usual care group ($P = 0.03$) (55). When reported, effects on lifestyle changes and medication adherence showed an overall pattern of small positive effects associated with nurse-managed protocols.

### Adherence to Protocols

Two studies (39, 52) reported data on nurses' adherence to treatment protocols. When compared with usual care, nurses instituted pharmacologic therapy for lipid management more often (39). O'Hare and colleagues (52) found that hypoglycemic agents and antihypertensives, including angiotensin-converting enzyme inhibitors, angiotensin II antagonists, and statins, were started or doses were increased by nurses following treatment protocols more often than in usual care groups.

### Adverse Effects

The included studies had few reports on adverse effects associated with nurse-managed protocols. Only 1 study on diabetes in a U.S. HMO (40) reported adverse effects. 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 ($P = 0.158$).

### Resource Use

Resource use was reported in only 3 studies (45, 47, 51). Houweling and colleagues (47) found total salary costs (±SE) to be significantly lower in the intervention group (€114.6 ± €50.4) than in the control group (€138.3 ± €48.3; $P < 0.001$). In this same study, total costs for medication were reported to be lower in the intervention groups (€136.3 ± €91.9) than in the control group (€149.0 ± €94.4; $P > 0.05$) at study completion.

Inpatient costs were reported to be substantially lower in 2 other studies. One study (45) estimated total inpatient costs for the intervention group at $869 535 compared with $1 702 682 for the control group ($P = 0.02$). The second study (51) reported decreases in costs by sex, with the intervention groups achieving a decrease of $606 for men and $888 for women. Further, total outpatient costs were reported at $1 237 270 in the nurse-managed protocol group compared with $1 381 900 in the control group ($P = 0.47$) (51).

### Subgroup Analysis

We did subgroup analyses comparing studies that were conducted in the United States compared with other countries, had targeted $HbA_{1c}$ alone compared with multiple conditions, and incorporated self-management plans compared with those that did not. These analyses showed greater effects on decreasing $HbA_{1c}$ level only for studies done on diabetes management in the United States (−0.92 vs. −0.23; $P = 0.01$). Treatment variability was reduced in these subgroups. Therefore, some variability in diabetes care may be explained by country or specificity of the intervention. For BP and cholesterol, subgroup analysis found no statistically significant differences in treatment effects. We planned to conduct subgroup analyses examining the intervention primarily by clinic visits compared with telephone calls, but variability in the results was insufficient.

## DISCUSSION

Nurse-managed protocols in the studies we examined had a consistently positive effect on chronically ill patients. Hemoglobin $A_{1c}$ levels decreased by approximately 0.4% (moderate strength of evidence [SOE]). Systolic and diastolic BP decreased by 4 mm Hg and 2 mm Hg, respectively (moderate SOE). Total cholesterol levels decreased by 0.24 mmol/L (9.37 mg/dL), and low-density lipoprotein cholesterol levels decreased by 0.31 mmol/L (12.07 mg/dL) (low SOE). Important differences were found in treatment effects across studies for most outcomes. Subgroup analyses explained little of this variability and showed differences only for effects on $HbA_{1c}$ level between non–U.S.-based and U.S.-based studies. Effects of nurse-managed protocols on lifestyle changes and medication adherence were reported infrequently, but when reported, they showed an overall pattern of small positive effects (low SOE).

The SOE was insufficient to estimate a treatment effect for all other outcomes: protocol adherence, adverse effects, and resource use. Indirect evidence (for example, proportion of patients prescribed the indicated medication) suggests reasonable adherence to the protocol by nurses. Although these studies showed protocol adherence by nurses in intervention groups compared with control participants, the SOE on nurse adherence was judged to be insufficient. Further, only 1 of the 18 studies reported adverse effects (40); therefore, the SOE was judged to be insufficient to determine the effect of nurse-managed protocols on adverse effects in treatment studies about chronic disease. Finally, resource use was reported in only 3 studies (45, 47, 51), so the evidence is insufficient to determine any effect.

Our study has many strengths, including a protocol-driven review, a comprehensive search, careful quality assessment, and rigorous quantitative synthesis methods. However, our report and the literature also have limitations. Because inclusion criteria required medication titration, we may have missed studies in which nurses had autonomy to practice in other capacities beyond their scope of practice. We did not include studies of inpatient settings in which nurses might often use protocols. The literature lacked detailed descriptions of the interventions and protocols used. Studies had limited descriptions of intervention intensity; treatment adherence; nurses' education levels, training, or supervision; protocol adherence; adverse effects; and resource use. Eleven of the 18 studies were done in countries outside the United States, which may limit applicability to U.S practices. Other performance measures were rarely reported. Studies were limited to the use of RNs; there was no report of using LPNs. Finally, the reported outcomes varied across studies and contributed to unexplained variability.

With changes in federal health policy, new models are needed to provide more accessible and effective chronic disease care. The implementation of a patient-centered medical home model will play a critical role in reconfiguring team-based care and will expand the responsibilities of team members. Our review shows that team approaches using nurse-managed protocols help improve health outcomes among patients with moderately severe diabetes, hypertension, and hyperlipidemia. In addition, RNs can successfully titrate medications according to protocols for these conditions. Similar results were found on the effects of quality improvement strategies on glycemic control in type 2 diabetes where case managers did not have to wait for physician approval to adjust medications (56). Further research is needed to understand the effects of nurse-managed protocols in caring for complex or unstable patients. **Supplement 8** (available at www.annals.org) presents a detailed table of identified evidence gaps and a framework for future research.

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 care. Team members, such as clinical pharmacists, may also be able to serve in similar capacities and in areas with limited health care resources (57). Thus, health care systems will need to balance the benefits and costs associated with each team member and determine who is best suited to take on these expanded roles. Results from our review suggest that nurse-managed protocols have positive

effects on outpatient care of adults with chronic conditions.

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