

# Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians

Amir Qaseem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Robert Rich, MD; Linda L. Humphrey, MD, MPH; Jennifer Frost, MD; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians\*

**Description:** The American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) jointly developed this guideline to present the evidence and provide clinical recommendations based on the benefits and harms of higher versus lower blood pressure targets for the treatment of hypertension in adults aged 60 years or older.

**Methods:** This guideline is based on a systematic review of published randomized, controlled trials for primary outcomes and observational studies for harms only (identified through EMBASE, the Cochrane Database of Systematic Reviews, MEDLINE, and ClinicalTrials.gov), from database inception through January 2015. The MEDLINE search was updated through September 2016. Evaluated outcomes included all-cause mortality, morbidity and mortality related to stroke, major cardiac events (fatal and nonfatal myocardial infarction and sudden cardiac death), and harms. This guideline grades the evidence and recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method.

**Target Audience and Patient Population:** The target audience for this guideline includes all clinicians, and the target patient population includes all adults aged 60 years or older with hypertension.

**Recommendation 1:** ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk for mortality, stroke, and cardiac events. (Grade: strong

recommendation, high-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.

**Recommendation 2:** ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for recurrent stroke. (Grade: weak recommendation, moderate-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.

**Recommendation 3:** ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for stroke or cardiac events. (Grade: weak recommendation, low-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.

*Ann Intern Med.* 2017;166:430-437. doi:10.7326/M16-1785 **Annals.org**  
For author affiliations, see end of text.  
This article was published at Annals.org on 17 January 2017.

**See also:**

Related article . . . . . 419

Editorial comment . . . . . 445

Summary for Patients . . . . . 1-26

Web-Only  
CME quiz

**H**ypertension, an elevation of systemic arterial blood pressure (BP), is a very common chronic disease in the United States. The overall prevalence of hypertension among U.S. adults is 29.0%, and it increases to 64.9% in adults aged 60 years or older (1). Hypertension was associated with a total of \$46 billion in health care services, medications, and missed days of work in the United States in 2011 (2).

\* This paper, written by Amir Qaseem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Robert Rich, MD; Linda L. Humphrey, MD, MPH; Jennifer Frost, MD; and Mary Ann Forciea, MD, was developed for the Clinical Guidelines Committee of the American College of Physicians (ACP) and the Commission on Health of the Public and Science of the American Academy of Family Physicians (AAFP). Individuals who served on the ACP Clinical Guidelines Committee from initiation of the project until its approval were Mary Ann Forciea, MD† (Chair); Nick Fitterman, MD (Vice Chair)‡; Michael J. Barry, MD‡; Cynthia Boyd, MD, MPH‡; Carrie A. Horwitch, MD, MPH‡; Linda L. Humphrey, MD, MPH‡; Alfonso Iorio, MD, PhD‡; Devan Kansagara, MD, MCR‡; Scott Manaker, MD, PhD‡; Robert M. McLean, MD‡; Sandeep Vijan, MD, MS‡; and Timothy J. Wilt, MD, MPH‡. Members of the AAFP's Commission on Health of the Public and Science were Patricia Czapp, MD (Chair)‡; Ada Denise Stewart, MD‡; David T. O'Gurek, MD‡; Joseph L. Perez, MD, MBA‡; Margot L. Savoy, MD, MPH‡; Kenneth W. Lin, MD, MPH‡; Jason M. Matuszak, MD‡; Ranit Mishori, MD, MHS‡; Daron W. Gersch, MD‡; Clare A. Hawkins, MD, MSct‡; Beulette Y. Hooks, MD‡; Robyn Liu, MD, MPH‡; Shannon Dowler, MD‡; Shani Muhammad, MD‡; Tobie-Lynn Smith, MD, MPH‡; James Stevermer, MD‡; Carolyn Gaughan‡; Vivian Jiang, MD‡; and Aisha Harris‡. Approved by the ACP Board of Regents on 16 July 2016. Approved by the AAFP Board of Directors on 20 July 2016.

† Author (participated in discussion and voting).

‡ Nonauthor contributor (participated in discussion but not voting).

Appropriate management of hypertension reduces the risk for cardiovascular disease, renal disease, cerebrovascular disease, and death (3-6). However, determining the most appropriate BP targets, particularly for adults aged 60 years or older, has been controversial. Debate about the goal for systolic BP (SBP) among adults treated for hypertension has intensified, especially in light of recent recommendations (7). In addition, when selecting BP targets for adults aged 60 years or older, clinicians need to consider comorbid conditions that could affect treatment choice. Treatments for hypertension include lifestyle modifications, such as weight loss, dietary modification, and increased physical activity, and antihypertensive medications, which commonly include thiazide-type diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), calcium-channel blockers, and  $\beta$ -blockers.

## GUIDELINE FOCUS AND TARGET POPULATION

The purpose of this American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) joint guideline is to present evidence-based recommendations on the benefits and harms of higher (<150 mm Hg) versus lower ( $\leq$ 140 mm Hg) SBP targets for the treatment of hypertension in adults aged 60 years or older. The target audience for this guideline includes all clinicians, and the target patient population includes adults aged 60 years or older with hypertension. These recommendations are based on a background evidence review (8) and systematic review sponsored by the U.S. Department of Veterans Affairs (VA) (9).

## METHODS

### Systematic Review of the Evidence

The evidence review was conducted by the Portland VA Health Care System Evidence-based Synthesis Program. The summary of methods for the evidence review can be found in the **Appendix** (available at [Annals.org](http://Annals.org)). Additional details are included in the accompanying background evidence review (8) and the full evidence report (9).

### Grading the Evidence and Developing Recommendations

This guideline was jointly developed by ACP's Clinical Guidelines Committee and representatives from AAFP according to ACP's guideline development process, details of which can be found in the methods paper (10). The committee used the evidence tables in the accompanying systematic review (8) and full report (9) when reporting the evidence and graded the recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method (Table).

### Peer Review

The VA evidence review was peer reviewed and posted on the VA Web site for public comments, and

**Table.** The American College of Physicians' Guideline Grading System\*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

\* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

the published review article was peer reviewed through the journal. The guideline had a peer-review process through the journal and was posted online for comments from ACP Regents and Governors, who represent physician members at the national and international level. The guideline was also reviewed by members of AAFP's Commission on Health of the Public and Science.

## BENEFITS OF TREATING HIGHER VERSUS LOWER BP TARGETS IN OLDER ADULTS

Across all trials, treating high BP in older adults was beneficial. However, most of the evidence came from studies of patients with moderate or severe hypertension (SBP >160 mm Hg) at baseline and, with treatment, achieved SBP targets greater than 140 mm Hg.

### Differing BP Targets

High-quality evidence showed reductions in all-cause mortality (relative risk [RR], 0.90 [95% CI, 0.83 to 0.98]; absolute risk reduction [ARR], 1.64), stroke (RR, 0.74 [CI, 0.65 to 0.84]; ARR, 1.13), and cardiac events (RR, 0.77 [CI, 0.68 to 0.89]; ARR, 1.25) for treating patients with a baseline SBP of 160 mm Hg or greater who achieved a target SBP of less than 150 mm Hg (11-21).

In studies with lower SBP targets (<140 mm Hg), low-quality evidence showed no statistically significant reduction in all-cause mortality (RR, 0.86 [CI, 0.69 to 1.06]; ARR, 0.80) or cardiac events (RR, 0.82 [CI, 0.64 to 1.00]; ARR, 0.94) (11-13, 20, 22, 23). For studies with lower BP targets, moderate-quality evidence showed a reduced risk for stroke (RR, 0.79 [CI, 0.59 to 0.99]; ARR, 0.49) compared with higher BP targets (11-13, 20, 22, 23). Many of these studies, however, did not achieve the targeted BP, and there was little difference between the intensive treatment and control groups. Therefore, these studies may not have been able to detect differences in clinical outcomes.

A subgroup analysis compared studies that achieved lower SBP targets (<140 mm Hg) with those that achieved higher SBP targets ( $\geq$ 140 mm Hg) (11-13, 20, 22-25). For these subgroups, high-quality evidence showed a similar risk reduction for mortality (RR for target  $\geq$ 140 mm Hg, 0.91 [CI, 0.84 to 0.99] vs. RR for tar-

get <140 mm Hg, 0.84 [CI, 0.74 to 0.95]) and cardiac events (RR for target  $\geq$ 140 mm Hg, 0.78 [CI, 0.68 to 0.93] vs. RR for target <140 mm Hg, 0.83 [CI, 0.70 to 0.94]). The relative reduction in stroke events was slightly larger for studies that achieved a target SBP of 140 mm Hg or greater (RR, 0.72 [CI, 0.62 to 0.82]) than those that achieved a target SBP of less than 140 mm Hg (RR, 0.81 [CI, 0.66 to 0.96]). These studies had marked clinical differences and significant statistical heterogeneity, which should temper confidence in the pooled results. Use of antihypertensive agents varied widely across studies: 7 used ACEIs or ARBs, 5 used calcium-channel blockers, and 6 used thiazide-like diuretics.

### Differing BP Targets in Patients With Transient Ischemic Attack or Stroke

Among patients with a history of stroke or transient ischemic attack (TIA), moderate-quality evidence showed that treating to an SBP of 130 to 140 mm Hg reduced stroke recurrence (RR, 0.76 [CI, 0.66 to 0.92]; ARR, 3.02) but not cardiac events (RR, 0.78 [CI, 0.61 to 1.08]) or all-cause mortality (RR, 0.98 [CI, 0.85 to 1.19]) (26, 27). Heterogeneity for this analysis was low.

### Differing BP Targets Based on Age

Low-quality evidence showed similar effects across different age groups (12-14, 16, 18-20, 22, 24, 26, 28, 29). A subgroup analysis of SPRINT (Systolic Blood Pressure Intervention Trial) that was not included in the evidence review showed that patients aged 75 years or older had lower all-cause mortality and nonstatistically significantly lower cardiovascular mortality, morbidity, and incidence of stroke with treatment to SBP targets less than 120 mm Hg compared with SBP targets less than 140 mm Hg (30).

### Differing BP Targets Based on Multiple Chronic Conditions

No trials assessed the effect of comorbidity on the benefits of more aggressive BP treatment. Low-quality evidence from subgroup analyses showed greater absolute benefit from more intensive BP treatment in patients with high cardiovascular risk (22, 29-31). However, patients with a high comorbidity burden were probably not included in the overall group of studies (8). Of the 21 trials included in the review, 14 excluded patients with heart failure, 11 excluded those with recent cardiovascular events, 17 excluded those with abnormal renal function, 12 excluded those with cancer or other life-limiting illness, 15 had criteria that would implicitly or explicitly exclude those with dementia or diminished functional status, and 7 excluded either all diabetic patients or those who required insulin. Although findings from ACCORD (Action to Control Cardiovascular Risk in Diabetes), which limited enrollment to patients with type 2 diabetes, found no reduction in mortality or major cardiovascular events with more intensive treatment, a subgroup analysis of 7 studies (12, 14, 18-20, 28, 29) in diabetic patients suggested that they were at least as likely to benefit from BP-lowering

treatment. This is probably related to the higher frequency of cardiovascular events seen in these patients.

### Treatment Effects According to Diastolic BP

Evidence was insufficient to determine the benefit of treating diastolic hypertension in the absence of systolic hypertension. Most trials assessed treatment outcomes based on SBP, and no trials included patients with a mean diastolic BP (DBP) greater than 90 mm Hg and a mean SBP less than 140 mm Hg.

## HARMS OF HIGHER VERSUS LOWER BP TARGETS IN OLDER ADULTS

Studies showed mixed findings for withdrawal due to adverse events. Treatment to lower BP targets increased withdrawals due to adverse events in 4 out of 10 trials (RR, 44% to 100%); cough and hypotension were the most frequently reported adverse events (13, 15, 17, 18, 20, 24, 27, 29, 31, 32). Low-quality evidence showed an increased risk for syncope associated with treatment to lower BP targets (achieved SBP range, 121.5 to 143 mm Hg) (RR, 1.52 [CI, 1.22 to 2.07]) (18, 23, 28). Low-quality evidence showed no difference in renal outcomes (including end-stage renal disease) for treatment to higher versus lower BP targets (13, 15, 16, 18, 20, 22-25, 28, 29, 32-34). Moderate-quality evidence showed no differences between treatment to higher versus lower BP targets in the degree of cognitive decline or dementia (18, 27, 35-39), fractures (40, 41), or quality of life (17, 42-44). Low-quality evidence showed no difference for treatment to higher versus lower BP targets on functional status (42) or the risk for falls (23, 40). A subgroup analysis of SPRINT showed a nonstatistically significant increase in the rate of serious adverse events, hypotension, syncope, electrolyte abnormalities, or acute kidney injury in patients aged 75 years or older who were treated to SBP targets less than 120 mm Hg versus SBP targets less than 140 mm Hg (28).

Although electrolyte disturbances are a common adverse effect of hypertension treatment in clinical practice, data were not presented on these abnormalities in the evidence review. Drugs to treat hypertension have well-known adverse effects, including hypokalemia, hyperkalemia, hyponatremia, hypotension, dizziness, headache, edema, erectile dysfunction, and cough.

### Effect of Age

Low-quality evidence showed no difference in adverse events, including unsteadiness, dizziness, and renal failure, in patients younger or older than 75 years (13, 23, 28).

### Effect of Multiple Chronic Conditions

No trials assessed the effect of comorbid conditions on harms.

## RECOMMENDATIONS

The **Figure** summarizes the recommendations and clinical considerations.

**Figure.** Summary of the American College of Physicians and American Academy of Family Physicians joint guideline on pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets.



Summary of the American College of Physicians and American Academy of Family Physicians Joint Guideline on Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets

Disease/Condition	Hypertension
Target Audience	All clinicians
Target Patient Population	Adults aged $\geq 60$ y with hypertension
Treatments Evaluated	Treatment to higher (<150 mm Hg) vs. lower ( $\leq 140$ mm Hg) SBP targets
Outcomes Evaluated	All-cause mortality, morbidity and mortality related to stroke, cardiac events, and harms
Benefits	Mortality, incidence of stroke, and cardiac events were all reduced with treatment.  Treating to a lower BP target did not further reduce mortality, quality of life, or functional status, but it did reduce the incidence of stroke and cardiac events.
Harms	Increased withdrawals due to adverse events with higher vs. lower BP targets  Increased cough, hypotension, and risk for syncope with treating to lower vs. higher BP targets  No difference between higher and lower BP targets for renal outcomes, cognitive outcomes, or falls and fractures
Adverse Effects	Some of the adverse effects associated with antihypertensive medications include (but are not limited to) the following:  Thiazide-type diuretics: electrolyte disturbances, gastrointestinal discomfort, rashes and other allergic reactions, sexual dysfunction in men, photosensitivity reactions, and orthostatic hypotension  ACEIs: cough and hyperkalemia  ARBs: dizziness, cough, and hyperkalemia  Calcium-channel blockers: dizziness, headache, edema, and constipation  $\beta$ -blockers: fatigue and sexual dysfunction
Recommendations	<i>Recommendation 1: ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk for mortality, stroke, and cardiac events. (Grade: strong recommendation, high-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.</i>  <i>Recommendation 2: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for recurrent stroke. (Grade: weak recommendation, moderate-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.</i>  <i>Recommendation 3: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for stroke or cardiac events. (Grade: weak recommendation, low-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.</i>
Clinical Considerations	Accurate measurement of BP is important before initiating treatment for hypertension. Some patients may have elevated BP in clinical settings, and ambulatory measurement may be appropriate.  Clinicians should consider treatment with nonpharmacologic options, including weight loss, dietary changes, and an increase in physical activity, initially or concurrently with pharmacologic treatment.  Many older adults may be taking various medications. Clinicians should consider treatment burden and drug interactions when deciding on treatment options.  When selecting pharmacologic therapy, clinicians should prescribe generic drugs where available.  Evidence for adults who are frail or those with multimorbidity is limited.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BP = blood pressure; SBP = systolic blood pressure.

*Recommendation 1: ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk for mortality, stroke, and cardiac events. (Grade: strong recommendation, high-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.*

High-quality evidence showed that treating hypertension in older adults to moderate targets (<150/90 mm Hg) reduces mortality (ARR, 1.64), stroke (ARR, 1.13), and cardiac events (ARR, 1.25). Most benefits apply to such adults regardless of whether they have diabetes. The most consistent and greatest absolute benefit was shown in trials with a higher mean SBP at baseline (>160 mm Hg). Any additional benefit from aggressive BP control is small, with a lower magnitude of benefit and inconsistent results across outcomes.

Although this guideline did not specifically address pharmacologic versus nonpharmacologic treatments for hypertension, several nonpharmacologic treatment strategies are available for consideration. Effective nonpharmacologic options for reducing BP include such lifestyle modifications as weight loss, such dietary changes as the DASH (Dietary Approaches to Stop Hypertension) diet, and an increase in physical activity. Nonpharmacologic options are typically associated with fewer side effects than pharmacologic therapies and have other positive effects; ideally, they are included as the first therapy or used concurrently with drug therapy for most patients with hypertension. Effective pharmacologic options include antihypertensive medications, such as thiazide-type diuretics (adverse effects include electrolyte disturbances, gastrointestinal discomfort, rashes and other allergic reactions, sexual dysfunction in men, photosensitivity reactions, and orthostatic hypotension), ACEIs (adverse effects include cough and hyperkalemia), ARBs (adverse effects include dizziness, cough, and hyperkalemia), calcium-channel blockers (adverse effects include dizziness, headache, edema, and constipation), and  $\beta$ -blockers (adverse effects include fatigue and sexual dysfunction).

Most of the included studies measured seated BP after 5 minutes of rest and used multiple readings. Clinicians should ensure that they are accurately measuring BP before beginning or changing treatment of hypertension. Assessment may include multiple measurements in clinical settings (for example, 2 to 3 readings separated by 1 minute in a seated patient who is resting alone in a room) or ambulatory or home monitoring (45).

*Recommendation 2: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for recurrent stroke. (Grade: weak*

*recommendation, moderate-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.*

Moderate-quality evidence showed that treating hypertension in older adults with previous TIA or stroke to an SBP target of 130 to 140 mm Hg reduces stroke recurrence (ARR, 3.02) compared with treatment to higher targets, with no statistically significant effect on cardiac events or all-cause mortality.

*Recommendation 3: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for stroke or cardiac events. (Grade: weak recommendation, low-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.*

An SBP target of less than 140 mm Hg is a reasonable goal for some patients with increased cardiovascular risk. The target depends on many factors unique to each patient, including comorbidity, medication burden, risk for adverse events, and cost. Clinicians should individually assess cardiovascular risk for patients. Generally, increased cardiovascular risk includes persons with known vascular disease, most patients with diabetes, older persons with chronic kidney disease with estimated glomerular filtration rate less than 45 mL/min/1.73 m<sup>2</sup>, those with metabolic syndrome (abdominal obesity, hypertension, diabetes, and dyslipidemia), and older persons. For example, among the included studies, SPRINT (23) defined patients with increased cardiovascular risk as those meeting at least 1 of the following criteria: clinical or subclinical cardiovascular disease other than stroke; chronic kidney disease, excluding polycystic kidney disease, with an estimated glomerular filtration rate of 20 to less than 60 mL/min/1.73 m<sup>2</sup> of body surface area; 10-year risk for cardiovascular disease of 15% or greater based on the Framingham risk score; or age 75 years or older. This trial found that targeting SBP to less than 120 mm Hg compared with less than 140 mm Hg in adults without diabetes or prior stroke, at high-risk for cardiovascular disease, and with a baseline SBP of less than 140 mm Hg significantly reduced fatal and nonfatal cardiovascular events and all-cause mortality. In contrast, ACCORD (40) included only adults with type 2 diabetes and found no statistically significant reduction in the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular events (RR, 0.94 [CI, 0.80 to 1.11]). This study did find a reduction in stroke events (RR, 0.58 [CI, 0.39 to 0.88]), but there were more serious adverse events associated with an SBP target of less than 120 mm Hg versus less than 140 mm Hg.

## AREAS OF INCONCLUSIVE EVIDENCE

### Treatment of Patients With Multiple Chronic Conditions

No trials assessed the relationship between multiple comorbid conditions and the benefits and harms of treating BP to different targets. Patients with a high comorbidity burden were probably not included in the overall group of studies. Many studies excluded patients with various comorbid conditions, such as diabetes, insulin use, recent coronary events, heart failure, or chronic kidney disease, and most studies had criteria that would implicitly or explicitly exclude those with dementia or diminished functional status.

### Treating According to DBP

Evidence was insufficient for targeting treatment according to DBP.

## MULTIPLE CHRONIC CONDITIONS: CLINICAL CONSIDERATIONS FOR ADULTS AGED 60 YEARS OR OLDER

Individual assessment of benefits and harms is particularly important in adults aged 60 years or older with multiple chronic conditions, several medications, or frailty. These patients might theoretically benefit from more aggressive BP treatment because of higher cardiovascular risks. However, they are more likely to be susceptible to serious harm from higher rates of syncope and hypotension, which were seen in some trials. Moreover, the absolute benefits of more aggressive BP treatment in elderly persons, those with multimorbidity, or those who are frail are not well-known, given limitations of the trials. These patients often receive multiple medications and are on drug regimens that are difficult to manage and increase the cost and risk for drug interactions. Indeed, most trials had exclusion criteria that implicitly or explicitly excluded patients who had dementia or diminished functional status. Few trials were available to compare patients with and without diabetes, which made drawing conclusions about relative treatment effects in these populations difficult. Whether the difference in results between SPRINT and ACCORD was because of diabetes status is unclear, but it is reasonable to rationalize that the benefits observed with the lower targets achieved in SPRINT most closely apply to patient populations without diabetes.

## HIGH-VALUE CARE

Most patients aged 60 years or older with an SBP of 150 mm Hg or greater who receive antihypertensive medications will have benefit with acceptable harms and costs from treatment to a BP target of less than 150/90 mm Hg. Although some benefit is achieved by aiming for lower BP targets, most benefit occurs with acceptable harms and costs in the pharmacologic treatment of patients who have an SBP of 150 mm Hg or greater. When prescribing drug therapy, clinicians should select generic formulations over brand-name drugs, which have similar efficacy, reduced cost, and

therefore better adherence (46). Clinicians should consider the patient's treatment burden when deciding on treatment options. Studies have correlated multiple doses of hypertensive medications with poorer medication adherence (47, 48). The balance of benefits and harms identified in our evidence report is based in part on rigorous and accurate assessment of BP. Some patients may have falsely elevated readings in clinical settings (known as "white-coat hypertension"). Therefore, it is important to ensure accurate BP measurement before initiating or changing treatment of hypertension. The most accurate measurements come from multiple BP measurements made over time.

From the American College of Physicians and University of Pennsylvania Health System, Philadelphia, Pennsylvania; Minneapolis Veterans Affairs Medical Center, Minneapolis, Minnesota; Community Care of the Lower Cape Fear, Wilmington, North Carolina; Oregon Health & Science University, Portland, Oregon; and American Academy of Family Physicians, Leawood, Kansas.

**Note:** Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

**Disclaimer:** The authors of this article are responsible for its contents, including any clinical or treatment recommendations.

**Financial Support:** Financial support for the development of this guideline comes exclusively from the ACP operating budget.

**Disclosures:** Authors followed the policy regarding conflicts of interest described at [www.annals.org/article.aspx?articleid=745942](http://www.annals.org/article.aspx?articleid=745942). Disclosures can also be viewed at [www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-1785](http://www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-1785). All financial and intellectual disclosures of interest were declared and potential conflicts were discussed and managed. Drs. Boyd, Kansagara, and Vijan participated in the discussion for this guideline, but they were recused from voting on the recommendations because of active indirect intellectual conflicts. Dr. Manaker participated in the discussion for this guideline but was recused from voting on the recommendations because of an active indirect financial conflict. A record of disclosures of interest and management of conflicts of interest is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at [www.acponline.org/clinical\\_information/guidelines/guidelines/conflicts\\_cgc.htm](http://www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm).

**Requests for Single Reprints:** Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106-1572; e-mail, [aqaseem@acponline.org](mailto:aqaseem@acponline.org).

Current author addresses and author contributions are available at [Annals.org](http://Annals.org).

## References

1. Yoon SS, Fryar CD, Carroll MD. Hypertension Prevalence and Control among Adults: United States, 2011-2014. NCHS Data Brief no. 220. Hyattsville, MD: National Center for Health Statistics; 2015.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29-322. [PMID: 25520374] doi:10.1161/CIR.000000000000152
3. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA*. 1967;202:1028-34. [PMID: 4862069]
4. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *BMJ*. 1992;304:405-12. [PMID: 1445513]
5. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA*. 1970;213:1143-52. [PMID: 4914579]
6. The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *Lancet*. 1980;1:1261-7. [PMID: 6104081]
7. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-20. [PMID: 24352797] doi:10.1001/jama.2013.284427
8. Weiss J, Freeman M, Low A, Fu R, Kerfoot A, Paynter R, et al. Benefits and harms of intensive blood pressure treatment in adults aged 60 years or older. A systematic review and meta-analysis. *Ann Intern Med*. 2017;166:419-29. doi:10.7326/M16-1754
9. Weiss J, Kerfoot A, Freeman M, Motu'apuaka M, Fu R, Low A, et al. Benefits and Harms of Treating Blood Pressure in Older Adults: A Systematic Review and Meta-analysis. VA ESP project no. 05-225. Washington, DC: U.S. Department of Veterans Affairs; 2015.
10. Qaseem A, Snow V, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. *Ann Intern Med*. 2010;153:194-9. [PMID: 20679562] doi:10.7326/0003-4819-153-3-201008030-00010
11. Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, et al; Cardio-Sis investigators. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet*. 2009;374:525-33. [PMID: 19683638] doi:10.1016/S0140-6736(09)61340-4
12. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*. 1998;351:1755-62. [PMID: 9635947]
13. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res*. 2008;31:2115-27. [PMID: 19139601] doi:10.1291/hypres.31.2115
14. Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. *Arch Intern Med*. 2000;160:211-20. [PMID: 10647760]
15. Amery A, Birkenhäger W, Brixko P, Bulpitt C, Clement D, Deruytere M, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet*. 1985;1:1349-54. [PMID: 2861311]
16. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887-98. [PMID: 18378519] doi:10.1056/NEJMoa0801369
17. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, et al; SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens*. 2003;21:875-86. [PMID: 12714861]
18. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*. 1991;265:3255-64. [PMID: 2046107]
19. Hara A, Thijs L, Asayama K, Jacobs L, Wang JG, Staessen JA. Randomised double-blind comparison of placebo and active drugs for effects on risks associated with blood pressure variability in the Systolic Hypertension in Europe trial. *PLoS One*. 2014;9:e103169. [PMID: 25090617] doi:10.1371/journal.pone.0103169
20. Ogiwara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, et al; Valsartan in Elderly Isolated Systolic Hypertension Study Group. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. *Hypertension*. 2010;56:196-202. [PMID: 20530299] doi:10.1161/HYPERTENSIONAHA.109.146035
21. Gong L, Zhang W, Zhu Y, Zhu J, Kong D, Pagé V, et al. Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens*. 1996;14:1237-45. [PMID: 8906524]
22. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575-85. [PMID: 20228401] doi:10.1056/NEJMoa1001286
23. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103-16. [PMID: 26551272] doi:10.1056/NEJMoa1511939
24. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370:829-40. [PMID: 17765963]
25. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A; FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens*. 2005;23:2157-72. [PMID: 16269957]
26. White CL, Szychowski JM, Pergola PE, Field TS, Talbert R, Lau H, et al; Secondary Prevention of Small Subcortical Strokes Study Investigators. Can blood pressure be lowered safely in older adults with lacunar stroke? The Secondary Prevention of Small Subcortical Strokes study experience. *J Am Geriatr Soc*. 2015;63:722-9. [PMID: 25850462] doi:10.1111/jgs.13349
27. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033-41. [PMID: 11589932]
28. Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, et al; SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet*. 2013;382:507-15. [PMID: 23726159] doi:10.1016/S0140-6736(13)60852-1
29. Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, et al; Telmisartan Randomised Assessment Study in ACE Intolerant subjects with Cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. 2008;372:1174-83. [PMID: 18757085] doi:10.1016/S0140-6736(08)61242-8
30. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al; SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. *JAMA*. 2016;315:2673-82. [PMID: 27195814] doi:10.1001/jama.2016.7050
31. Ruggenenti P, Fassi A, Ilieva A, Iliev IP, Chiurciu C, Rubis N, et al; BENEDICT-B Study Investigators. Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial. *J Hypertens*. 2011;29:207-16. [PMID: 21243736]

32. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-9. [PMID: 11565518]
33. Voyaki SM, Staessen JA, Thijs L, Wang JG, Efstratopoulos AD, Birkenhäger WH, et al; Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Follow-up of renal function in treated and untreated older patients with isolated systolic hypertension. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *J Hypertens*. 2001;19:511-9. [PMID: 11288822]
34. Peralta CA, McClure LA, Scherzer R, Odden MC, White CL, Shlipak M, et al. Effect of intensive versus usual blood pressure control on kidney function among individuals with prior lacunar stroke: a post hoc analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) randomized trial. *Circulation*. 2016;133:584-91. [PMID: 26762524] doi:10.1161/CIRCULATIONAHA.115.019657
35. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, et al; HYVET investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol*. 2008;7:683-9. [PMID: 18614402] doi:10.1016/S1474-4422(08)70143-1
36. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al; Systolic Hypertension in Europe Investigators. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med*. 2002;162:2046-52. [PMID: 12374512]
37. Williamson JD, Launer LJ, Bryan RN, Coker LH, Lazar RM, Gerstein HC, et al; Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Investigators. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. *JAMA Intern Med*. 2014;174:324-33. [PMID: 24493100] doi:10.1001/jamainternmed.2013.13656
38. Skoog I, Lithell H, Hansson L, Elmfeldt D, Hofman A, Olofsson B, et al; SCOPE Study Group. Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE). *Am J Hypertens*. 2005;18:1052-9. [PMID: 16109319]
39. Bird AS, Blizard RA, Mann AH. Treating hypertension in the older person: an evaluation of the association of blood pressure level and its reduction with cognitive performance. *J Hypertens*. 1990;8:147-52. [PMID: 2162877]
40. Margolis KL, Palermo L, Vittinghoff E, Evans GW, Atkinson HH, Hamilton BP, et al. Intensive blood pressure control, falls, and fractures in patients with type 2 diabetes: the ACCORD trial. *J Gen Intern Med*. 2014;29:1599-606. [PMID: 25127725] doi:10.1007/s11606-014-2961-3
41. Peters R, Beckett N, Burch L, de Vernejoul MC, Liu L, Duggan J, et al. The effect of treatment based on a diuretic (indapamide) ± ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET). *Age Ageing*. 2010;39:609-16. [PMID: 20573778] doi:10.1093/ageing/afq071
42. Applegate WB, Pressel S, Wittes J, Luhr J, Shekelle RB, Camel GH, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. *Arch Intern Med*. 1994;154:2154-60. [PMID: 7944835]
43. Fletcher AE, Bulpitt CJ, Thijs L, Tuomilehto J, Antikainen R, Bossini A, et al; Syst-Eur Trial Investigators. Quality of life on randomized treatment for isolated systolic hypertension: results from the Syst-Eur Trial. *J Hypertens*. 2002;20:2069-79. [PMID: 12359987]
44. Wiklund I, Halling K, Rydén-Bergsten T, Fletcher A. Does lowering the blood pressure improve the mood? Quality-of-life results from the Hypertension Optimal Treatment (HOT) study. *Blood Press*. 1997;6:357-64. [PMID: 9495661]
45. Siu AL; U.S. Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;163:778-86. [PMID: 26458123] doi:10.7326/M15-2223
46. Choudhry NK, Denberg TD, Qaseem A; Clinical Guidelines Committee of American College of Physicians. Improving adherence to therapy and clinical outcomes while containing costs: opportunities from the greater use of generic medications: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2016;164:41-9. [PMID: 26594818] doi:10.7326/M14-2427
47. Nuesch R, Schroeder K, Dieterle T, Martina B, Battegay E. Relation between insufficient response to antihypertensive treatment and poor compliance with treatment: a prospective case-control study. *BMJ*. 2001;323:142-6. [PMID: 11463685]
48. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med*. 1990;150:1881-4. [PMID: 2102668]

**Current Author Addresses:** Dr. Qaseem: American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106-1572.

Dr. Wilt: Minneapolis Veterans Affairs Medical Center, One Veterans Drive (111-0), Minneapolis, MN, 55417.

Dr. Rich: Bladen Medical Associates, 300 A East McKay Street, PO Box 517, Elizabethtown, NC 28337.

Dr. Humphrey: Veterans Affairs Portland Health Care System, 3710 SW U.S. Veterans Hospital Road, Portland, OR 97201.

Dr. Frost: American Academy of Family Physicians, 11400 Tomahawk Creek Parkway, Leawood, KS 66211.

Dr. Forciea: University of Pennsylvania Health System, 3615 Chestnut Street, Philadelphia, PA 19104.

**Author Contributions:** Conception and design: A. Qaseem, L.L. Humphrey.

Analysis and interpretation of the data: A. Qaseem, T.J. Wilt, L.L. Humphrey, J. Frost, M.A. Forciea.

Drafting of the article: A. Qaseem, T.J. Wilt, R. Rich, L.L. Humphrey, J. Frost.

Critical revision of the article for important intellectual content: A. Qaseem, T.J. Wilt, R. Rich, L.L. Humphrey, J. Frost, M.A. Forciea.

Final approval of the article: A. Qaseem, T.J. Wilt, R. Rich, L.L. Humphrey, J. Frost, M.A. Forciea.

Statistical expertise: A. Qaseem, T.J. Wilt.

Administrative, technical, or logistic support: A. Qaseem.

## APPENDIX: DETAILED METHODS

The evidence review was conducted by the Portland VA Health Care System Evidence-based Synthesis Program to address the following key questions (KQs):

KQ 1: In adults aged 60 years or older, what are the health outcome effects of differing BP targets?

KQ 1b: In patients who have suffered a TIA or stroke, does treatment of BP to specific targets affect health outcomes?

KQ 2: How does age modify the benefits of differing BP targets?

KQ 3: How does the patient burden of comorbid conditions modify the benefits of differing BP targets?

KQ 4: What are the harms of targeting lower BP in older patients? Do the harms vary with age?

KQ 5: Do the harms of targeting lower BP vary with patient burden of comorbid conditions?

### Search Strategy

The reviewers searched EMBASE and the Cochrane Database of Systematic Reviews from database inception through January 2015, MEDLINE through September 2016, and ClinicalTrials.gov to identify studies that were in progress or unpublished. Observational studies were excluded from analysis of such health outcomes as mortality, stroke, and cardiovascular events. For additional information, including inclusion and exclusion criteria, refer to the accompanying article (8) and full report (9).

## Meta-analysis and Individual-Patient Data

### Meta-analysis

The reviewers conducted a meta-analysis on study-level data using the random-effects model. They also conducted individual-patient data meta-analysis to assess treatment according to age subgroups.

### Quality Assessment

The quality of studies was assessed using the Cochrane risk-of-bias tool (49). The evidence reviewers graded the quality of evidence using the Agency for Healthcare Research and Quality system (50).

### Population

Adults aged 60 years or older with a diagnosis of hypertension were studied.

### Interventions Evaluated

The interventions evaluated included treatment to higher (<150 mm Hg) versus lower ( $\leq$ 140 mm Hg) SBP targets.

### Comparators

The comparator was less intensive BP treatment.

### Outcomes

Evaluated outcomes included all-cause mortality; cardiac events (myocardial infarction and sudden cardiac death); morbidity and mortality related to stroke; and harms, including cognitive impairment, quality of life, falls, fractures, syncope, functional status, hypotension, acute kidney injury (defined as the doubling of serum creatinine or need for renal replacement therapy), medication burden, and withdrawal due to adverse events.

### Timing

Outcomes were assessed in the long-term (>6 months) for KQs 1, 2, and 3 and any time frame for KQs 4 and 5.

### Study Design

Controlled study designs (randomized, controlled trials and nonrandomized, controlled trials) (KQs 1, 2, 3, 4 and 5) and cohort studies (KQs 4 and 5) were included. Case reports; case series; randomized, controlled trials with less than 6-month follow-up; and controlled before-after studies were excluded.

### Peer Review

The VA evidence review was sent to invited peer reviewers and posted on the VA Web site for public comments, and the published review article was peer reviewed through the journal. The guideline had a peer-review process through the journal and was posted online for comments from ACP Regents and Governors, who represent physician members at the national level. It was also reviewed by members of AAFP's Commission on Health of the Public and Science.

### Web-Only References

49. Higgins JPT, Green S, eds. Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1. The Cochrane Collaboration. 2008. Accessed at <http://handbook.cochrane.org> on 21 December 2016.
50. Berkman ND, Lohr KN, Ansari M, McDonagh M, Balk E, Whitlock E, et al. AHRQ Methods for Effective Health Care Grading the

Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville: Agency for Healthcare Research and Quality; 2008.