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Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults:

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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†The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Abstract

OBJECTIVE—To review the literature systematically and perform meta-analyses to address these questions: 1) Is there evidence that self-measured blood pressure (BP) without other augmentation is superior to office-based measurement of BP for achieving better BP control or for preventing adverse clinical outcomes that are related to elevated BP? 2) What is the optimal target for BP lowering during antihypertensive therapy in adults? 3) In adults with hypertension, how do various antihypertensive drug classes differ in their benefits and harms compared with each other as first-line therapy?

METHODS—Electronic literature searches were performed by Doctor Evidence, a global medical evidence software and services company, across PubMed and EMBASE from 1966 to 2015 using key words and relevant subject headings for randomized controlled trials that met eligibility criteria defined for each question. We performed analyses using traditional frequentist statistical and Bayesian approaches, including random-effects Bayesian network meta-analyses.

RESULTS—Our results suggest that: 1) There is a modest but significant improvement in systolic BP in randomized controlled trials of self-measured BP versus usual care at 6 but not 12 months, and for selected patients and their providers self-measured BP may be a helpful adjunct to routine office care. 2) systolic BP lowering to a target of <130 mm Hg may reduce the risk of several important outcomes including risk of myocardial infarction, stroke, heart failure, and major cardiovascular events. No class of medications (i.e., angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers, or beta blockers) was significantly better than thiazides and thiazide-like diuretics as a first-line therapy for any outcome.

Keywords

ACC/AHA Clinical Practice Guidelines; antihypertensive drug class; blood pressure; cardiovascular disease; Evidence Review Committee; home blood pressure monitoring; hypertension; meta-analysis; risk reduction; targets; treatment outcomes

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, based on systematic methods to evaluate and classify evidence, provide a cornerstone of quality cardiovascular care. In response to reports from the Institute of Medicine (1,2) and a mandate to evaluate

new knowledge and maintain relevance at the point of care, the ACC/ AHA Task Force on Clinical Practice Guidelines (Task Force) modified its methodology (3–5).

Evidence Review

The Task Force recognizes the need for objective, independent evidence review committees (ERCs) that include methodologists, epidemiologists, clinicians, and biostatisticians who systematically survey, abstract, and assess the evidence to address systematic review questions posed in the PICOTS format (P=population, I=intervention, C=comparator, O=outcome, T=timing, S=setting) (2,4–6). Practical considerations, including time and resource constraints, limit the ERCs to evidence that is relevant to key clinical questions and lends itself to systematic review and analysis that could affect the strength of corresponding recommendations. Recommendations developed by the writing committee on the basis of the systematic review are marked “SR”.

Relationships With Industry and Other Entities

The ACC and AHA sponsor the guidelines without commercial support, and members volunteer their time. The Task Force avoids actual, potential, or perceived conflicts of interest that might arise through relationships with industry or other entities (RWI). All ERC members are required to disclose current industry relationships or personal interests, from 12 months before initiation of the writing effort. The ERC chair and all ERC members may not have any relevant RWI (Appendix 1). For transparency, ERC members’ comprehensive disclosure information is available online. Comprehensive disclosure information for the Task Force is available online.

Glenn N. Levine, MD, FACC, FAHA Chair, ACC/AHA Task Force on Clinical Practice Guidelines

PART 1: SELF-MEASURED VERSUS OFFICE-BASED MEASUREMENT OF BLOOD PRESSURE IN THE MANAGEMENT OF ADULTS WITH HYPERTENSION

Introduction: Part 1

Although the awareness and treatment of hypertension has increased steadily over the past decade, it is estimated that approximately 50% of patients are still not adequately controlled (7). The AHA, together with the American Society of Hypertension and the Preventive Cardiovascular Nurses Association, published a scientific statement in 2008 supporting the use of self-measured blood pressure (BP) to help monitor response to medication, and to confirm suspected diagnoses of white coat or masked hypertension (8). Additional indications for self-measured BP cited in the “2013 European Society of Hypertension/European Society of Cardiology Guidelines for the Management of Arterial Hypertension” included characterization of episodic hypotension, and identification of true- and false-resistant hypertension (9). There are several potential advantages to self-measured BP, such as raising patient awareness of how their BP responds to medication or dietary

changes, decreasing physician inertia to adjust medication when the office-measured BP is high, and decreasing costs related to office visits for BP management (9,10).

When patients are trained about proper technique and use appropriately sized BP cuffs, the information provided by self-measured BP has strong prognostic significance. Observational studies suggest that the association of self-measured BP with target organ damage, such as left ventricular hypertrophy, is comparable to ambulatory blood pressure monitoring (ABPM), and superior to office-measured BP (11,12). Self-measure BP is also more strongly associated with cardiovascular morbidity and mortality than office-measured BP (13).

Several randomized controlled trials (RCTs) have examined whether the use of self-measured BP is associated with an improvement in clinical outcomes compared with usual care (14–29). There is substantial heterogeneity among studies, as many focused on self-measured BP alone, whereas others included varying degrees of additional support (e.g., education, counseling, telemedicine). A systematic review and meta-analysis by Uhlig et al. in 2013 demonstrated that self-measured BP monitoring alone versus usual care conferred a modest reduction in systolic and diastolic BPs (–3.9 mm Hg and –2.4 mm Hg, respectively) (14). However, although the benefit was seen at 6 months, it did not extend to 12 months.

Since the 2013 analysis by Uhlig et al., 2 studies were published that compared self-measure BP versus office-measured BP (19,29). In addition, not all of the studies examined reported enough detail about the variability of the reported BP estimates. The Task Force recognized the need for a subsequent review of self-measured BP by an independent ERC to inform recommendations about its potential use in the evaluation and management of patients with hypertension.

Methods: Part 1

The ERC conducted this meta-analysis to address these clinical questions posed by the writing committee:

1. Is there evidence that self-measured BP without other augmentation is superior to office-measured BP for achieving better BP control?
2. Is there evidence that self-measured BP without other augmentation is superior to office-measured BP for preventing adverse clinical outcomes that are related to elevated BP?

This meta-analysis complied with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (30) and with the recommendations of the “ACCF/AHA Clinical Practice Guideline Methodology Summit Report” (5).

Search Strategy: Part 1

Eligible studies were identified by employees of Doctor Evidence using PubMed and EMBASE. Doctor Evidence is a global medical evidence software and services company. RCTs published in English from January 1, 1966, through February 12, 2015, were included. The search strategy is found in Table 1.1 in the Online Data Supplement.

Eligibility Criteria

RCTs were included that compared self-measured BP alone to usual care in adults (≥ 18 years of age) who were being evaluated and/or treated for hypertension. All studies had a minimum of 6 months follow-up. Studies of adults with end-stage renal disease and pregnant women were excluded, as were studies in which ABPM was the only form of self-monitoring. Studies that used self-measured BP plus additional support had substantial heterogeneity in study design; therefore, we restricted the analyses to self-measured BP interventions that were not augmented. Interventions were considered augmented if the trial protocol required additional direct feedback from the study staff to the participants randomized to self-measured BP based on their home BP measurements, beyond what was given in the usual care arm. Studies that required adjustment of the medical regimen between clinic visits in response to self-measured BP results were also considered augmented. Contact between the study participants and staff that was optional or required only for safety concerns was not considered augmentation.

The prespecified primary outcome was change in systolic BP at 6 and 12 months. Additional outcomes that were measured included the proportion of the study population whose office-measured BP was controlled (<140/90 mm Hg), medication adherence, number of medications prescribed or mean doses of medication, and incidence rates for myocardial infarction (MI), stroke, acute decompensated heart failure, and coronary or peripheral revascularization. Outcomes were required to be reported at ≥ 6 months with enough detail to determine the variability of estimates (e.g., standard error, standard deviation, or confidence intervals [CI]). Outcomes at ≥ 14 months were rare and not included in the analysis.

Methods of Review

To determine eligibility for inclusion in the meta-analysis, 2 members of the ERC independently reviewed each study. Disagreements were resolved by consensus or by discussion with the remaining members of the ERC. Data extraction was performed using the DOC Data 2.0 software platform (Doctor Evidence, 2016. DOC Data, Version 2.0. Santa Monica, CA: Doctor Evidence, LLC) using a standard template for predefined data points. Included studies were single-extracted by an evidence analyst with software validation/data entry error prevention. Each data point was verified against the source article by a quality control analyst (single extraction with sequential quality control). Discrepancies were resolved by the project methodologist and/or the chief medical officer. Subsequent dataset-level quality control (to identify outliers and ensure consistency of data across studies) was performed by an evidence audit specialist. An ontology specialist managed the naming of outcomes based on author-reported names and definitions.

Abstracted data from each study included the authors, year of publication, sample size, inclusion and exclusion criteria, study design, participant characteristics, duration of follow-up, systolic and diastolic BP at baseline and end of study, change in BP, proportion of the study population whose BP was controlled, secondary outcomes including medication adherence, number and classes of medications prescribed, and cardiovascular event rates. The Cochrane Collaboration Risk of Bias Tool was used to evaluate risk of bias (31). A

study was given an overall rating of low-to-intermediate risk of bias if the RCT was not thought to be at high risk of bias for any domain of study quality.

Statistical Analysis

We performed a random-effects meta-analysis using the DerSimonian-Laird method for outcomes adequately reported by 4 studies. When available, the intervention effect on change in systolic BP from baseline was used for analysis, unadjusted if that was reported. Otherwise, the intervention effect on follow-up systolic BP was used, again unadjusted if that was reported. If intervention effects were not reported, but change from baseline in each group was reported with sample sizes and estimated variability, those estimates were used to estimate the intervention effect. If only follow-up values were reported with sample sizes and estimates of variability, those values were used to estimate the intervention effect. CIs were used as estimates of variability if standard deviations or standard errors were not reported. Studies that did not report estimates of variability were excluded. We adjusted for follow-up because some studies reported results after only 6, 9, or 12 months, and 2 studies reported results after both 6 and 12 months.

Results: Part 1

Study Characteristics—We screened 181 abstracts, evaluated 43 full-text articles, and included 13 RCTs. The 13 RCTs contributed data from 4021 participants, with sample sizes ranging from 62 to 552 participants. The characteristics of the studies and the participants are presented in the Online Data Supplement Part 1, (Table 1.2). The mean age ranged from 47 to 69 years, and approximately 50% of participants were women.

Of the 13 studies, 6 contributed data for 12 months of follow-up, 1 for 9 months of follow-up, 4 for 6 months of follow-up, and 2 reported outcomes at both 6 and 12 months of follow-up. Given the nature of the studies, none of the participants were blinded. Two trials were excluded from the analyses (1 study because only 9-month systolic BP was reported (26) and the other because SBP variability was not reported (25)) but were included in the analyses related to the proportion of participants achieving BP control.

All of the studies recruited participants with an elevated office-measured BP, typically defined as $\geq 140/90$ mm Hg. However, the severity and type of hypertension differed across studies. For example, 1 study recruited patients who had been diagnosed with hypertension for at least 1 year and did not further restrict based on severity (18). However, $>70\%$ of the participants were already controlled on medication at study initiation. Another study restricted enrollment to adults who had already been treated for hypertension and were not at goal (21). An additional study screened all eligible patients with ABPM (19). Potential participants whose mean ambulatory systolic BP was $<135/85$ mm Hg were excluded, thus minimizing the number of participants with white coat hypertension. In contrast, another study excluded adults who were on >2 BP medications at baseline (16).

Study Outcomes: Office Systolic BP—Ten trials were included for the analysis of office-measured BP (see Online Data Supplement Part 1 Table 1.2; Figure 1). Two trials contributed both 6- and 12-month outcomes, 2 contributed only 6-month outcomes, and 6

contributed only 12-month outcomes. We fit an adjustment for length of follow-up (6 or 12 months). We did not adjust for the within-study variation (2 studies included both 6- and 12-month measurements (21,23)), but sensitivity analyses limiting all studies to a single measurement were not qualitatively different.

The association of self-measured BP with systolic BP varied across the studies. The results are provided in Online Data Supplement Part 1; Figure 1. Two of the studies were associated with a statistically significant worsening of systolic BP, 5 studies reported a significant improvement in systolic BP, and 5 reported no significant difference in systolic BP between self-measured BP and office-measured BP. Effect sizes ranged from a 7.4 mm Hg worsening of systolic BP to a 6.5 mm Hg improvement in systolic BP with self-measured BP compared with office-measured BP.

In the full meta-analysis, self-measured BP was associated with a 4.9 mm Hg (95% CI: 1.3 to 8.6 mm Hg) greater reduction in office systolic BP at 6 months compared with office-measured BP. However, the effect diminished by 12 months to 0.1 mm Hg (95% CI: -2.54 to 2.8 mm Hg), which was not statistically significant. The funnel plot for residuals from the adjusted model showed modest evidence of heterogeneity (see Online Data Supplement Part 1, Figure 1.2). There may be some bias against publication of null and negative studies.

Participants randomized to self-measured BP were asked to measure their BP at home 1 to 5 times a week, depending on the study. Subsequent decisions regarding medical therapy were left to participants' clinicians in most of the studies. For example, in 1 study, participants mailed their BP logs to the study investigators, who then forwarded the results to the participants' providers (17). Treating physicians were encouraged to use their patients' BP logs for monitoring rather than seeing them in the office but were still free to decide the frequency of office visits. In another study, participants randomized to self-measured BP were asked to measure their BP weekly (19). The data were transmitted automatically to a website where participants could track their readings. Participants' providers were encouraged, but not mandated, to access the website weekly. How frequently providers accessed the website was not reported.

In contrast, in other studies, providers whose patients participated were expected to follow a specific protocol in response to BP measurements (16). Participants in both arms were expected to be seen in the office 1 and 2 months after the baseline visit, and then every 2 months thereafter. Medication decisions were based on a target diastolic BP of 80 to 89 mm Hg. When the diastolic BP was >89 mm Hg, providers were given a stepped protocol dictating how to titrate medication. When the diastolic BP was <80 mm Hg, providers withdrew medication. As a result, 25.6% of the self-measured BP participants versus 11.3% office-measured BP participants permanently stopped treatment, suggesting that many of the participants had white coat hypertension. However, of the 55 participants randomized to self-measured BP who stopped medication for a diastolic BP <80 mm Hg, only 64.7% maintained a diastolic BP <85 mm Hg for the remainder of the study.

Study Outcomes: Percent Achieving Target BP

Of the 6 studies reporting the proportion of participants achieving their target BP, 1 study was excluded because the percent achieving target in the intervention arm was determined using self-measurements, while the percent achieving target in the control arm was determined using office measurements (22). For the grouped analysis, only end of study values were used.

Results from the 5 remaining studies were similar (see Online Data Supplement Part 1, Figure 1.3). None reported a significant intervention effect. Consistent with the office-measure BP results, there was a slightly more positive response at 6 months than 12 months, but neither was significant. One study was heavily weighted, as its regression model produced an estimate with relatively narrow confidence limits (18).

Additional Outcomes

Other outcomes included clinical events and medication usage.

Clinical Events—Events, including stroke, MI, total mortality and cardiovascular mortality were considered for possible analysis. Except for total mortality, no data on any specific clinical event were reported by 4 studies and no analysis was attempted. Total mortality was reported by 4 studies, but the number of events was small and details of how mortality data were ascertained were unclear. None of the 4 studies reported a significant difference, and the overall risk ratio was not different from 1.0.

Medication Requirement: Number of Medications—Assessment of BP medication requirements was hetero-geneous among trials reporting this outcome. Five studies reported either the number of medications, the number of “defined doses,” or a medication score: these were combined in an outcome labeled “number of medications” for analysis. Two indicated more medication for the control arm (16,22), 1 for the intervention arm (19), and 2 were equal (23,29).

Adherence and Pill Counts—Adherence was assessed in several ways, including self-report, pill counts, and monitoring events medication system; however, because the measures were qualitatively different, and some did not have associated measures of variability, they could not be combined in a meta-analysis.

Summary of Other Outcomes—No conclusions could be made regarding clinical events. For medication requirement, data from 4 studies indicated no effect on the mean number of medications at 6 months. The data for adherence were not reported in way that allowed reliable quantitative assessment.

Risk of Bias

Assessment of the funnel plots showed no heterogeneity among the studies reporting 6-month outcomes, but some heterogeneity among studies with 12-month outcomes. The results suggest a possible publication bias against studies with longer follow-up and null findings (see Online Data Supplement Part 1, Figure 1.2). It was not possible to blind the

participants to their treatment allocation. Given the objective nature of the study outcomes, it is less likely that this would lead to bias.

Several studies reported >20% loss to follow-up (15,18,20,22,25,26). The loss to follow-up was balanced between the 2 treatment arms, although was of borderline significance with greater loss to follow-up in the self-measured BP versus control arm in 1 of the studies ($p = 0.08$) (18).

Discussion: Part 1

In this meta-analysis of 13 RCTs, we found that self-measured BP without additional support versus office-measured BP was associated with a modest improvement in systolic BP at 6 months, but no difference in systolic BP at 12 months. In our analysis of 5 RCTs, we found no significant difference in the proportion of participants whose BP was controlled between the self-measured BP and office-measured BP arms.

Taken together, the results suggest that self-measured BP without additional support provides only a modest and short-term improvement in BP control. Our results are similar to a previously published meta-analysis (14), which reported that systolic BP was 3.9 mm Hg lower among adults randomized to self-measured BP compared with office-measured BP. We included several of the same studies as this meta-analysis; however, we also excluded several studies from this analysis that were not published in English or did not adequately report BP variability. In addition, 2 studies (19,29) were published after the 2013 report. We found insufficient data to draw conclusions about the association of self-measured BP with clinical events. Measurement and reporting of other secondary outcomes such as medication prescription and adherence was inconsistent.

Variations in study design may have diminished a potential association between self-measured BP and improved BP control and should be considered. For example, in 1 study, a substantially higher proportion of adults who were randomized to self-measured BP versus office-measured BP permanently discontinued medication for a diastolic BP <80 mm Hg (per study protocol), suggesting that many of the participants likely had white coat hypertension and would be less likely to derive any benefit from ongoing self-measured BP (16). In contrast, another study—which reported a 4.3-mm Hg improvement in systolic BP with self-measured BP—used a more rigorous screening strategy by performing ABPM in all potentially eligible participants, and only including adults whose systolic BP remained elevated (19).

We found that the modest benefit of self-measured BP was seen only at 6 months and not at 12 months. Study design, rather than a diminished effect of self-measured BP over time, is likely the primary explanation for our findings. Of all the studies included in the analysis, only 2 showed significantly less favorable control with self-measured BP than office-measured BP, and both were in the group with 12-month outcomes (16,24). As previously mentioned, in 1 of these studies, BP treatment was determined by a stepped protocol, so that medication was discontinued when the diastolic BP was <80 mm Hg (16). Such a limited definition of BP control resulted in significantly more participants in the self-measured BP arm being taken off their medication. The difference in BP between the

2 treatment arms was similar at 6 and 12 months. Another study reported a nonsignificant trend toward less favorable BP control with self-measured BP than office-measured BP and had also used a strict dosing protocol (22). As a result, patients in the self-measured BP arm were taking on average 1 fewer medications than in the office-measured BP arm. In contrast, in a study where adults randomized to self-measured BP mailed their BP logs to their physicians but often did not receive feedback on their results (24), adults randomized to the office-measured BP group had significantly more extra visits (5.3 versus 1.4) to see their physicians, which may have improved factors such as medication adherence. In the remaining group of studies that reported 12-month outcomes, all but 1 study showed either a significant benefit or at least a trend toward improved control with self-measured BP (Figure 1).

BP control rates in both arms of some studies were remarkably low. Therefore, it is difficult to know whether provider and/or patient inertia may explain the only modest benefit seen with self-measured BP, rather than inherent limitations of self-measured BP itself. For example, in 1 study, 52% and 46% of the self-measured BP and office-measured BP participants, respectively, were still not on medication by the end of the study, despite a mean office BP of 151/93 mm Hg (24). In another study, <20% of participants in both arms were started on medication despite having a mean systolic BP >140 mm Hg (20). For those started on medication, it took an average of 6 months for medication to be initiated after an abnormal BP reading.

However, several studies that combined self-measured BP with additional support, and thus were not included in this meta-analysis, have reported meaningful and sustained improvements in BP control. For example, 1 study randomized 450 patients with uncontrolled BP at baseline to office-measured BP versus a program with home BP telemonitoring with pharmacist management (27). Adults randomized to the intervention experienced an additional 6.6 mm Hg lowering of systolic BP compared with usual care, which was maintained for 6 months after the intervention ended. A second study also demonstrated a substantial improvement in BP control among adults randomized to a pharmacist-led, telemonitoring program compared with office-measured BP; those randomized to the intervention experienced a -12.4 mm Hg (95% CI: -16.3 to -8.6%) larger reduction in systolic BP (28). Importantly, the results were even more pronounced among adults with diabetes mellitus or chronic kidney disease (CKD) (-15.4 mm Hg larger decrease; 95% CI: -21 to -9.8). In addition, the intervention arm had more email and telephone contacts and greater medication intensification than the office-measured BP arm. The results suggest that self-measured BP can serve as a valuable component of a multidisciplinary approach to the treatment of hypertension. As a result, the Centers for Disease Control and Prevention encourages the use of self-measured BP with additional support (32).

Limitations: Part 1

This meta-analysis has several limitations. As with any meta-analysis, we may be limited by unpublished data. There were differences in study design even among the studies that used only self-measured BP, which may have limited our ability to detect more substantial

improvements in BP control with self-measured BP. We were also limited by our inability to comment on outcomes other than systolic BP, such as medication adherence, or clinical outcomes, such as end-organ damage or clinical events.

Conclusions: Part 1

In summary, we found a modest but significant improvement in systolic BP in RCTs of self-measured BP versus office-based BP. However, the improvement was not sustained for longer than 6 months. Well-run studies of self-measured BP, in conjunction with additional support, have demonstrated more substantial improvements in BP control, but study design is highly variable. Our results suggest that, for selected patients and their providers, self-measured BP may be a helpful adjunct to routine office care.

PART 2: TARGETS FOR BLOOD PRESSURE LOWERING DURING ANTIHYPERTENSIVE THERAPY IN ADULTS

Introduction: Part 2

High BP has been long recognized as the single most common risk factor for cardiovascular disease burden (33–36). The treatment and management of hypertension has been documented to significantly reduce morbidity and mortality (37–40) and is also among the most common reasons for ambulatory clinic visits among adults world-wide (41). Thus, clinical practice guidelines represent an essential component of management and control of high BP, and such guidelines with recommended target BP levels have been associated with shift in population BP to lower levels and disease risks (42). It is also essential that such guidelines are based on current and clear evidence from clinical studies and should be based on rigorous systematic evidence reviews for specific critical questions for the interpretation of the evidence and the crafting of the specific clinical recommendations as recommended by the 2011 report from the Institute of Medicine on the development of trustworthy clinical guidelines (1). The goals of the ACC/AHA writing committee include the development of guidelines, standards, and policies that promote optimal patient care and cardiovascular health.

There have been 8 recent meta-analyses addressing the issues of BP reduction and target BP levels for the treatment of hypertension (37–39,43–47). Although treatment of hypertension was associated with improved outcomes in all 8 meta-analyses, the optimal target BP remains unclear. In the current systematic review and meta-analysis, we sought to determine the optimal targets for BP lowering during antihypertensive therapy in adults.

Methods: Part 2

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and to recommendations of the “ACCF/AHA Clinical Practice Guideline Methodology Summit Report” (5,30)

Search Strategy and Information Sources

An electronic literature search was performed by Doctor Evidence, a global medical evidence software and services company, across PubMed and EMBASE from 1966 to April 13, 2015, using key words and relevant subject headings for “hypertension” combined with terms for the interventions of interest (see Online Data Supplement Part 2, Table 2.1). An additional PubMed search was performed through May 6, 2015. SPRINT (Systolic Blood Pressure Intervention Trial) was included in November 2015, and SPS3 (Secondary Prevention of Small Subcortical Strokes Trial) was included in April 2016 at the request of the ERC (48,49). The ERC also searched bibliographies of recent, relevant meta analyses (37–39,50).

Eligibility Criteria

RCTs were considered for inclusion if they met the following eligibility criteria (see Online Data Supplement Part 2, Table 2.2): included adults (> 18 years of age) with primary hypertension or hypertension due to CKD; if the intervention included a target BP that was more “intensive” or “lower” than a “standard” or “higher” target BP in the comparator arm; and outcomes included all-cause mortality, cardiovascular mortality, major cardiovascular events, MI, stroke, heart failure, or renal outcomes. Trials were excluded if the primary intent of the study was not specifically to treat or lower BP, were observational studies, or included <100 randomized participants or <400 person years of follow-up, and a minimum of 12 months of follow-up. Relevant studies were excluded if they did not report outcomes of interest with enough detail to estimate variability.

Study Selection

A trained medical librarian screened the titles and abstracts of studies against predefined selection criteria using a software environment with features such as color coding and ranking of relevant key words. A second medical librarian also performed quality control using these tools. The chief medical officer and the project methodologist reviewed all included abstracts and a random sample of excluded abstracts, managed discrepancies between librarians, and decided on studies of uncertain eligibility. Members of the ERC were divided into pairs and performed dual independent review of full text articles in the DOC Library software platform (Doctor Evidence. 2016. DOC Library. Santa Monica, CA: Doctor Evidence, LLC). Disagreements were resolved by consensus between the 2 reviewers and the ERC chair.

Data Extraction and Quality Assessment

Data extraction was performed using the DOC Data 2.0 (Doctor Evidence, 2016, DOC Data, Version 2.0, Santa Monica, CA: Doctor Evidence, LLC) software platform using a standard template for predefined data points. Included studies were single-extracted by an evidence analyst with software validation/data entry error prevention and with each data point verified against the source article by a quality control analyst (single extraction with sequential quality control). Discrepancies were resolved by the project methodologist and/or chief medical officer. Subsequent dataset-level quality control (to identify outliers and ensure consistency of data across studies) was performed by an evidence audit specialist. An

ontology specialist managed the naming of outcomes based on author-reported names and definitions.

For each included study, this information was abstracted: study design, participant characteristics (age, race and ethnicity, sex, comorbid conditions), and duration of follow-up. Risk of bias was assessed for each study included using the Cochrane Risk of Bias tool (31), which examines 7 sources of bias (randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective outcome reporting, and other potential biases). Studies were considered to have low risk of bias if there was low risk of bias for all domains or plausible bias was unlikely to alter results. Studies were considered to have high risk of bias if there was high risk of bias for 1 key domains and the plausible bias seriously weakened confidence in results.

Data Synthesis and Analysis

We extracted study results based on target BP and examined them based on intent-to-treat analysis. BP-lowering targets varied by study but, for this meta-analysis, participants assigned to the lower BP target composed the lower BP target group and the higher BP target composed the standard therapy group. Major cardiovascular events were included in the analysis only if defined and reported by the trial as a composite outcome and included events such as cardiovascular death, stroke, MI, and heart failure. Heart failure definitions varied but included these measures: acute decompensated heart failure, revascularization or hospitalization for congestive heart failure (CHF) or death due to heart failure, CHF of New York Heart Association class II or higher, CHF of New York Heart Association class III or IV requiring admission to hospital, CHF of New York Heart Association class III or higher or echocardiography determining left ventricular ejection fraction <40%, or hospitalization for CHF necessitating therapy with an inotropic agent, vasodilator, angiotensin-converting enzyme inhibitor (ACEI), increased dose of diuretic, ultrafiltration, or dialysis. Fatal and nonfatal events were included in the outcomes for MI and stroke. Renal events include these composite of outcomes: end-stage renal disease or death secondary to end-stage renal disease, doubling of serum creatinine, 50% reduction in glomerular filtration rate, long-term dialysis, kidney transplantation, progression of CKD, renal failure, and renal failure in absence of acute reversible cause.

For each outcome, we calculated the relative risk (RR) and 95% CI from the number of events and participants. First, we examined risk of each outcome for any lower BP target versus any standard BP target, then we examined the effect of a lower systolic BP target <130 mm Hg versus any higher BP target for all outcomes. In prior guidelines, there was insufficient evidence to demonstrate benefit of a BP goal <140/90 mm Hg (73). Given the completion of additional studies with lower target BP goals, we examined available evidence to determine whether a lower BP goal conferred additional benefit either in the general population or in a specific subpopulation. The lower goal of 130 mm Hg was selected because it was the lower limit of high-normal BP and was the goal BP set by other guidelines for certain subpopulations. There were an adequate number of studies with a BP target of 130 mm Hg to study the question.

We performed random-effects meta-analysis using the DerSimonion-Laird method for outcomes adequately reported by 3 studies. The percentage of variability across studies, which was attributable to heterogeneity rather than chance, was measured using the I^2 statistic, where $I^2 < 30\%$ was considered low heterogeneity and $> 50\%$ was considerable heterogeneity (51,52). The presence of publication bias was assessed using funnel plots for each outcome. We used the Begg rank correlation test to calculate Kendall's Tau and p value to examine funnel plot asymmetry (53). The Egger weighted linear regression method uses the effect size and standard error to quantify bias (54). Predefined subgroups of interest included sex, race and ethnicity, age, and comorbidity. Although many of the included studies reported subgroup results, no subgroup of interest was reported by at least 3 studies for any of the 7 outcomes examined in the current meta-analysis; therefore, subgroup meta-analyses were not conducted. We compiled and reviewed published subgroup findings for the 7 outcomes in the present study. To further understand the effect of a lower target BP versus any higher target BP on subgroups of interest, we conducted sensitivity analyses to limit the number of studies included and examined the effect in studies, which included: 1) only patients with diabetes mellitus; 2) only patients with CKD; or 3) a study population with mean age ≥ 60 years at baseline.

All analyses were performed using an online platform (Doctor Evidence. 2016. DOC Data, Version 2.0. Santa Monica, CA: Doctor Evidence, LLC) that incorporated R statistical software using Metafor (55).

Results: Part 2

See the Online Data Supplement for detailed information.

Study Selection

A total of 33 publications from 15 studies were considered for inclusion (Figure 2). Fourteen of the publications were subsequently excluded from the primary analyses for these reasons: outcomes reported in another publication, outcome presented by subgroup, no outcome of interest, no in-trial results presented, intent-to-treat analysis not presented (per protocol results only), or event counts unavailable (see Online Data Supplement Part 2, Table 2.3).

Study Characteristics

Online Data Supplement Part 2, Table 2.4 describes the inclusion and exclusion criteria and BP targets for each of the trials included in the present meta-analysis. Publication dates ranged from 1998 through 2015. Target BPs varied for the lower and standard BP groups with 9 studies having a systolic BP target < 130 mm Hg for the lower therapy group (48,49,56–64). Many of the studies included patients with comorbid conditions such as diabetes mellitus, CKD, or were at high risk for cardiovascular disease or progression to end-stage renal disease. Most studies excluded those with prior or recent MI or stroke, secondary hypertension, CHF, or other serious illnesses.

Mean follow-up time ranged from 1.6 to 8.4 years (Online Data Supplement Part 2, Table 2.5). The proportion of male participants in each study ranged from 37.5% to 75.0%, and proportion of nonwhite participants ranged from 7.3% to 100% among 10 studies reporting

race and ethnicity. Mean age at baseline ranged from 36.3 years to 76.6 years, and 8 studies reported mean participant age of 60 years at baseline. In 3 studies each, all participants had diabetes mellitus or CKD.

Study protocols were summarized and compared in the Online Data Supplement, Part 2, Table 2.6 The frequency of participant contact during follow up differed by study with many studies including more frequent visits in the months post randomization, then decreasing in frequency after reaching a designated time such as 4 or 6 months. With the exception of ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, which had more frequent visits for participants in the lower BP target group initially, studies maintained similar frequency of contact for participants in the lower and standard BP target groups.

Risk of Bias Within and Across Studies

Overall, the studies included in the analyses showed low or unclear risk of bias. Of the 15 included trials, 12 showed high risk of bias for the blinding of study participants and personnel because blinding was not possible or performed (49,56–62,64–70), 1 study showed unclear risk of bias, and 2 studies had low risk of bias in this domain because they used identical placebo tablets for the randomized groups (71,72). Two studies showed high risk of bias due to inadequately addressing incomplete outcome data (57,58,60). Included studies showed low or unclear risk of bias for all other domains.

Data Synthesis and Analysis of Results

When we examined results for the 7 outcomes for trials of any lower BP target versus any standard or higher BP target (Online Data Supplement Part 2, Table 2.7), we found that greater BP lowering significantly reduced the risk of major cardiovascular events (RR: 0.81; 95% CI: 0.70 to 0.94), MI (RR: 0.86; 95% CI: 0.76 to 0.99), stroke (RR: 0.77; 95% CI: 0.65 to 0.91), and heart failure (RR: 0.75; 95% CI: 0.56 to 0.99), with a marginally significant reduction in all-cause mortality (RR: 0.89; 95% CI: 0.77 to 1.02). Heterogeneity between studies was lowest for MI and renal events but there was significant heterogeneity found between all studies for all-cause mortality. There were no indications for publication bias as measures of funnel plot asymmetry did not reach significance for any of the outcomes.

When we limited our analyses to RCTs with a systolic BP target <130 mm Hg in the lower BP target group compared with any higher BP target (Online Data Supplement Part 2, Table 2.8), the risk reductions were modestly attenuated but remained significant for major cardiovascular events (RR: 0.84; 95% CI: 0.73 to 0.99) and stroke (RR: 0.82; 95% CI: 0.70 to 0.96) and marginally significant for MI (RR: 0.85; 95% CI: 0.73 to 1.00) and all-cause mortality (RR: 0.92; 95% CI: 0.79 to 1.06). Heterogeneity between studies was lowest for MI, stroke, and renal events and highest for major cardiovascular events and heart failure although it was not statistically significant. There were no indications of publication bias as measures of funnel plot asymmetry did not reach significance for any of the outcomes. Additional details about individual studies included for each outcome can be found in the Online Data Supplement Part 2, Tables 2.9–2.16. These supplemental tables show the calculated relative risk for all studies included for each outcome, as well as information about the sensitivity analyses such as studies included and heterogeneity statistics.

Sensitivity Analyses

Three studies had populations comprised of patients with diabetes mellitus, 3 study populations were comprised of patients with CKD, and 8 trials had study populations with a mean age ≥ 60 years. We found similar estimates of effect for all sensitivity analyses (see Online Data Supplement Part 2, Table 2.17). The strongest effect was seen among patients with diabetes mellitus where greater BP lowering reduced the risk of stroke by 44% (RR: 0.56; 95% CI: 0.42 to 0.74). Although there was no indication of heterogeneity between studies, Egger's Regression Test indicated significant funnel plot asymmetry ($p=0.04$). Among studies with a mean age ≥ 60 years, the lower BP target resulted in findings similar to the overall results with significant reductions in major cardiovascular events, stroke, heart failure, and marginally significant reduction in MI.

A summary table of effect estimates and subgroup analyses reported by each study for the 7 outcomes reported in this meta-analysis have been compiled (see Online Data Supplement Part 2, Table 2.18). However, subgroup results could not be pooled in a meaningful way. Among the subgroup analyses reported by individual studies, there were no significant findings.

Discussion: Part 2

In this meta-analysis, we examined the reduction in risk of morbidity and mortality for 7 outcomes, comparing results from trials that randomly assigned individuals to lower targets versus standard targets for BP reduction. We found that greater BP lowering significantly reduced the risk of major cardiovascular events, MI, stroke, and heart failure. To determine whether an optimal target for BP reduction could be identified, we also examined reduction in risk of these outcomes for RCTs with a systolic BP target <130 mm Hg in the lower BP target group and again found a reduced risk of stroke and major cardiovascular events with marginally significant reductions in risk of MI and all-cause mortality. Limiting the analyses to studies that included only participants with diabetes mellitus or CKD or with a mean participant age ≥ 60 years had little impact on the findings.

Our results are largely in agreement with the findings of other recent meta-analyses (see Online Data Supplement Part 2, Table 2.19 (37–39,43–47,50)). The studies used various methodological techniques to examine the extent to which the benefits of BP-lowering treatments for prevention of cardiovascular disease differed by baseline BP level (39) or among subgroups such as people with diabetes mellitus (44) or older adults (45,48).

There was agreement across meta-analyses that greater BP lowering appears to be most beneficial for the reduction in risk of major cardiovascular events, MI, stroke, and heart failure. Two studies reported a significant reduction in the risk of all-cause mortality (39,46), 3 studies reported reduction in cardiovascular mortality (37,44,47), but no meta-analysis found a significant reduction in the risk of renal events for the lower BP target group compared with a higher BP target group.

Identifying the most appropriate targets for BP to reduce cardiovascular morbidity and mortality has been elusive. In 2007, an National Heart, Lung, and Blood Institute expert panel concluded that it would be important to test the hypothesis that a lower systolic BP

goal could reduce clinical events more than a standard BP reduction goal. Several large recent RCTs sought to answer that question by selecting systolic BP treatment targets of <120 mm Hg (49,61,63,64) or <130 mm Hg (48,56–60,62). The results of our meta-analysis have shown that BP lowering to a target of <130 mm Hg may significantly reduce the risk of several important outcomes. The results appear to have similar benefits for people regardless of comorbid conditions and age.

This meta-analysis has several limitations that should be acknowledged. First, as is the case with many meta-analyses, the results may be limited by unpublished data. Additionally, there are differences in time periods during which the studies were conducted as well as differences in study designs including differences in the BP reduction targets and differences in hypertension treatment protocols that may have limited our ability to detect benefits of BP lowering. Outcome definition also varied by study. Finally, although a lower BP target did not result in additional benefit beyond what was seen for the general population for populations with diabetes mellitus or CKD, or in studies with a mean study population age 60 years, it is possible that we have an incomplete understanding. Due to variable reporting of subgroup findings, we were unable to pool reported subgroup findings from published reports in a meaningful way and the previously reported subgroup analyses summarized in the Online Data Supplement Part 2, Table 2.18) should be interpreted with caution as they may represent the findings from only 1 study for a given outcome and subgroup.

The consideration of target systolic BP for the treatment of high BP represents a critical clinical question of the management of hypertension, but also a parameter of controversy. The 2014 report from the panel members appointed to the Eighth Joint National Committee included a rigorous evidence-based methodology for assessing the results of randomized controlled trials identifying strong support for treating hypertensive persons aged 60 years to a BP goal of <150/90 mm Hg (73), as opposed to the traditional 140/90 mm Hg from other recommendations during the same time period (40,74). Because the panel only used a systematic review of original studies, systematic reviews and meta-analyses were not included in the formal evidence review. Thus, the systematic review of the evidence by the different groups identified different target BP levels and subsequent confusion in clinical recommendations (75,76). The current systematic review includes new evidence from clinical studies and presents the results in a rigorous meta-analysis. Likewise, the recent clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians restricted the evidence to patients aged 60 years with a recommended less aggressive approach to start treatment for patients who have persistent systolic BP 150 mm Hg to achieve a target of <150 mm Hg to reduce risk for stroke, cardiac events, and death in individuals 60 years of age (77). Further, the “2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure” recommends a BP goal of <130/80 mm Hg for patients with hypertension and at increased risk of developing cardiovascular disease (78). The recommendation is based on evidence of new RCT data and the fact that BP measurements as generally taken in the office setting are typically 5 to 10 mm Hg higher than research measurements. Our current meta-analysis includes the extensive body of evidence from additional patients supporting the benefit of more aggressive control in the prevention of cardiovascular disease and stroke.

Conclusions: Part 2

Proper treatment of high BP is critical due to the health risks associated with uncontrolled or insufficiently controlled BP. The results of our meta-analysis are consistent with other recent meta-analyses which demonstrate that BP lowering significantly reduced the risk of cardiovascular morbidity and mortality regardless of meta-analytic method, comorbid condition, or mean age of study participant. Additionally, we have shown that BP lowering to a target of <130 mm Hg may reduce the risk of several important outcomes including risk of MI, stroke, heart failure, and major cardiovascular events.

PART 3: FIRST-LINE ANTIHYPERTENSIVE DRUG CLASS COMPARISONS IN ADULTS**Introduction: Part 3**

Hypertension is a leading cause of death worldwide, and its prevalence has increased dramatically over the past 2 decades (34). Elevated BP levels contribute to more than two thirds of the burden of stroke and half the burden of ischemic heart disease (79). Antihypertensive therapies have established benefits in reducing the risk for major cardiovascular events; however, the benefits of any one class of antihypertensive therapies as a first-line therapy, relative to other classes, is still debated. Several meta-analyses have examined these questions, but additional contemporary trials not included in prior publications may provide an improved understanding of the relative benefits for each class of antihypertensive therapies.

We conducted a network meta-analysis of trials that compared any 2 classes of antihypertensive therapies used as first-line pharmacotherapy for high BP including thiazide and thiazide-like diuretics (THZs), ACEIs, angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), and beta blockers. Our objective was to examine the comparative benefits and harms of different antihypertensive classes in adults with hypertension.

Methods: Part 3

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and to recommendations of the “ACCF/AHA Clinical Practice Guideline Methodology Summit Report” (5,30).

Search Strategy and Information Sources

An electronic literature search was performed by Doctor Evidence, a global medical evidence software and services company, across PubMed and EMBASE from 1966 to March 30, 2015, using key words and relevant subject headings for “hypertension” combined with terms for the interventions of interest Online Data Supplement Part 3, Table 3.1.

Eligibility Criteria

RCTs were considered for inclusion if they met the eligibility criteria outlined in the Online Data Supplement (Part 3, Table 3.1.1; Figure 3) according to the systematic review question framework. Study population criteria required that study participants be adults 18 years

of age with primary hypertension or hypertension due to CKD. The study interventions must have used as first-line therapy for hypertension: THZs, ACEIs, ARBs, CCBs, or beta blockers. Comparators were the same as described for the interventions as long as they represented a different class of antihypertensive medication than the intervention. There were 8 outcome criteria that we established including: all-cause mortality, cardiovascular mortality, heart failure, stroke, MI, composite cardiovascular events, major adverse cardiac events, and renal outcomes. Outcomes must have occurred after at least 48 weeks of follow-up. Heart failure, stroke, and MI outcomes included fatal and nonfatal events; composite cardiovascular outcomes included MI, stroke, CHF, acute coronary syndrome, peripheral artery disease, angina, and/or coronary revascularization; major adverse cardiac events included cardiovascular outcomes and mortality; and renal outcomes included end-stage renal disease, dialysis, doubling of creatinine, halving of estimated glomerular filtration rate, and/or dialysis. The definition of some outcomes varied across studies; however, within trials, the outcomes were the same across treatments.

Additional criteria required that studies include at least 100 randomized patients or at least 400 patient years of follow-up to ensure adequate sample size. These are commonly used thresholds for restricting randomized controlled trials in systematic reviews (80). Studies of combination therapy were allowed as long as the combinations contained 1 drug of the classes listed previously and 2 classes were compared.

Study Selection

A trained medical librarian screened the titles and abstracts of studies against predefined selection criteria using a software environment with features such as color coding and ranking of relevant key words across PubMed and EMBASE from 1966 to March 30, 2015. A second medical librarian performed quality control using the same tools. The chief medical officer and the project methodologist reviewed all included abstracts and a random sample of excluded abstracts, managed discrepancies between librarians, and decided on studies of uncertain eligibility. Members of the ERC were divided into pairs and performed dual independent review of full-text articles in the DOC Library software platform (Doctor Evidence. 2016. DOC Library. Santa Monica, CA: Doctor Evidence, LLC) Disagreements were resolved through discussion between the 2 reviewers and the ERC chair.

Data Extraction and Quality Assessment

Data extraction was performed using the DOC Data 2.0 (Doctor Evidence. 2016. DOC Data, Version 2.0. Santa Monica, CA: Doctor Evidence, LLC) software platform using a standard template for predefined data points. Authors were contacted regarding discrepancies and missing information. Included studies were single extracted by an evidence analyst with software validation and data entry error prevention and with each data point verified against the source article by a quality control analyst (single extraction with sequential quality control). Discrepancies were resolved by the project methodologist and/or the chief medical officer. Subsequent dataset-level quality control (to identify outliers and ensure consistency of data across studies) was performed by an evidence audit specialist. An ontology specialist managed the naming of outcomes based on author-reported names and definitions. Although a systematic assessment of the quality of studies was not conducted, assessment of bias,

using Cochrane's collaboration tool for assessing risk of bias, was used selectively on individual studies when/if needed during the analytic process. Because of the large number of studies and the extent of heterogeneity associated with other factors (which will be assessed), a comprehensive review of risk of bias was impractical.

Data Synthesis and Analysis

Random-effects Bayesian network meta-analyses were conducted to compare multiple antihypertensive treatments within the same statistical model. The unit of analysis was at the individual study level. We conducted a network meta-analysis where the randomization of comparisons within trials are maintained (the direct comparisons), while simultaneously, all available comparisons of treatments across trials are also used (indirect comparisons) (80). The network meta-analysis allows us to combine all available direct and indirect comparisons of antihypertension medication classes (rather than be limited to a standard meta-analysis reporting only direct pairwise comparisons). For dichotomous outcomes the logarithm of the RR for each trial and its standard error was calculated. We fit a linear mixed model to the log RRs from each trial with a random effect specific to each pair of treatments. Pooled network estimates were reported at RR and 95% credible intervals (CrI). Model fit and model comparisons was assessed using convergence, residual deviance, leverage, deviance information criteria, and analysis of heterogeneity (81).

We conducted stratified analysis among population subgroups including those with and without diabetes mellitus, men, women, blacks, and age-strata (< 65 years of age). The number of studies for the subgroup analyses was limited and, in some cases, there were not enough data to run the network analysis and report pooled network risk estimates for a particular outcome and subgroup. Although many of the individual studies may report risk estimates for subgroup analyses, if they do not also report the binary data then we did not include them in our analyses.

Analyses were performed using an online platform (Doctor Evidence, 2016, DOC Data, Version 2.0, Santa Monica, CA: Doctor Evidence, LLC) using the integrated R Project for Statistical Computing package gemtc.

Results: Part 3

A total of 144 publications were considered for inclusion in this study as shown in Figure 3. Eighty-six publications were subsequently excluded from the primary analyses. Most were excluded because they did not include an outcome of interest, but others were excluded for these reasons: outcomes reported in another publication, outcome presented by subgroup only, intent-to-treat analysis not presented (per protocol results only), or results were provided as rates and event counts were unavailable.

The network diagrams for each of the outcomes show the geometry of the relationships between classes (see Online Data Supplement Part 3, Figures 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, and 3.8). They show which classes (nodes) have been compared head to head in randomized controlled trials and which have been compared indirectly by having been compared in separate trials to common comparators. Depending on the outcome, the indirect comparisons contributing to the pooled network estimates used information from 3 to 40 studies. In each

of the network diagrams, the trials that are included in each pairwise comparison are labeled above the arrow, while the pooled pairwise RR (95% CI) for the direct comparison are shown below the arrow. For example, in the first network diagram for all-cause mortality (see Online Data Supplement Part 3, Figure 3.1), ACEIs are common comparator for ARBs, CCBs, THZs, and beta blockers. For each pair-wise comparison, the arrowhead points to the class of antihypertensive medication for which a higher RR would reflect an increased risk of the outcome.

Online Data Supplement Part 3, Table 3.2, presents a summary of the trials and the demographic and clinical characteristics of the participants. A total of 152,379 patients are included in these meta-analyses with an average of 3.5 years of follow-up. Studies were published between 1985 and 2014. The number of patients randomized per trial ranged from 102 to 33,357, with the largest being ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). Many of the studies were conducted among individuals with comorbid conditions including diabetes mellitus, end-stage renal disease, patients on dialysis, or with stage 3 CKD (i.e., those with an estimated glomerular filtration rate <60 mL/min/m²). Fourteen trials included a THZ arm, 25 had an ACEI arm, 9 had an ARB arm, 28 had a CCB arm, and 10 had a beta blockers arm. Each trial's class-to-class comparisons are shown in the network diagrams for each outcome. Online Data Supplement Part 3, Table 3.3, reports the number of study participants and all-cause mortality events in each of the included trials by antihypertensive medication class. ALLHAT contributed the largest number of trial participants in the CCB, ACEI, and THZ classes for all of our outcomes. The ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm trial) contributed the largest number of participants randomized to beta blockers for all-cause mortality, cardiovascular mortality, MI, and heart failure; with the Losartan Intervention For Endpoint reduction study (82) contributing the largest number of participants in the beta blockers group for stroke and cardiovascular composite events.

The pooled network risk estimates (which incorporates estimates from both direct and indirect comparisons) associated with all-cause mortality are provided in Online Data Supplement Part 3, Figure 3.9. These results show all the relative treatment effect estimates of each of the antihypertensive medication class compared to THZ. Online Data Supplement Part 3, Figure 3.9.1 shows the pooled network relative risks associated with each of the first-line antihypertensive medication classes compared to THZ for all of the outcomes. The RRs of all-cause mortality were 1.0 (95% CrI: 0.95–1.1) for ACEIs; 0.99 (95% CrI: 0.88–1.1) for ARBs; 1.1 (95% CrI: 0.98–1.2) for beta blockers; and 0.97 (95% CrI: 0.90–1.1) for CCBs, compared with THZs (see Online Data Supplement Part 3, Figure 3.9). The RRs of cardiovascular mortality were 1.1 (95% CrI: 0.92–1.3) for ACEIs; 1.1 (95% CrI: 0.87–1.5) for ARBs; 1.2 (95% CrI: 0.98–1.4) for beta blockers; and 1.0 (95% CrI: 0.86–1.2) for CCBs, compared with THZ (see Online Data Supplement Part 3, Figure 3.10). Only the 20% increased risk of cardiovascular mortality associated with of beta blockers compared with THZ was (borderline) significant. Also, the risk of cardiovascular mortality was higher (and borderline significant) for beta blockers compared with CCBs with a RR of 1.2 (95% CrI: 0.98–1.4; see Online Data Supplement Part 3, Table 3.4).

The RRs of CHF were 1.2 (95% CrI: 0.91–1.5) for ACEIs; 1.1 (95% CrI: 0.79–1.6) for ARBs; 1.3 (95% CrI: 0.94–1.7) for beta blockers; and 1.3 (95% CrI: 1.0–1.6) for CCBs, compared with THZs (see Online Data Supplement Part 3, Figure 3.11). Patients on CCBs had a 30% greater risk of CHF compared with those on THZs. The RRs of stroke were 1.1 (95% CrI: 0.98–1.4) for ACEIs; 1.1 (95% CrI: 0.88–1.4) for ARBs; 1.3 (95% CrI: 1.1–1.6) for beta blockers; and 0.96 (95% CrI: 0.83–1.2), for CCB, compared with THZs (see Online Data Supplement Part 3, Figure 3.12). There was also a borderline significant increased risk of stroke for ACEIs and beta blockers compared with CCBs with RRs of 1.2 (95% CrI: 1–1.4) and 1.4 (95% CrI: 1.1–1.7), respectively (see Online Data Supplement Part 3, Table 3.5). The RRs of cardiovascular events were 1.1 (95% CrI: 0.96–1.3) for ACEIs; 1 (95% CrI: 0.89–1.2) for ARBs; 1.2 (95% CrI: 1–1.4) for beta blockers; and 1.1 (95% CrI: 0.98–1.2) for CCBs, compared with THZs (see Online Data Supplement Part 3, Figure 3.13). The risk of cardiovascular events was reduced (and borderline significant) for ARBs compared with beta blockers with a RR of 0.88 (95% CrI: 0.78–1.0; see Online Data Supplement Part 3, Table 3.6). There were no significant risks of all-cause mortality, MI, or renal outcomes for any of the antihypertensive medication class to class comparisons.

To investigate whether these results were consistent by race, we conducted stratified analyses among studies with predominantly black study populations (defined as studies reporting subgroup analysis in blacks or having populations with at least 85% black) or which published race-specific analyses. We observed no significant differences in all-cause mortality, cardiovascular mortality, MI, CHF, cardiovascular events, or renal outcomes among blacks for any of the class-by-class comparisons. For all-cause mortality, there were 4 studies among blacks (ALLHAT, African American Study of Kidney Disease and Hypertension [AASK], Agarwal, and Sareli; see Online Data Supplement Part 3, Table 3.7). The RRs of all-cause mortality among blacks were 1.1 (95% CrI: 0.96–1.2) for ACEIs; 1.3 (95% CrI: 0.87–2.0) for beta blockers; and 0.98 (95% CrI: 0.88–1.1) for CCBs, compared with THZs (see Online Data Supplement Part 3, Figure 3.14). For cardiovascular mortality, there were also 4 studies among blacks (ALLHAT, AASK, Losartan Intervention For Endpoint reduction [LIFE], and Agarwal; see Online Data Supplement Part 3, Table 3.8). The RRs of cardiovascular mortality among blacks were 1.0 (95% CrI: 0.68–1.6) for ACEIs; 1.2 (95% CrI: 0.40–3.5) for ARBs; 0.81 (95% CrI: 0.35–1.8) for beta blockers; and 1.0 (95% CrI: 0.65–1.5) for CCBs, compared with THZs (see Online Data Supplement Part 3, Figure 3.15). For MI, there were 3 studies among blacks (ALLHAT, LIFE, and Agarwal; see Online Data Supplement Part 3, Table 3.9). The RRs of MI among blacks were 1.1 (95% CrI: 0.42–2.7) for ACEIs; 1.4 (95% CrI: 0.1–20) for ARBs; 0.62 (95% CrI: 0.06–5.9) for beta blockers; and 1.0 (95% CrI: 0.39–2.6) for CCBs, compared with THZs (see Online Data Supplement Part 3, Figure 3.16). For CHF, there were 3 studies among blacks (ALLHAT, AASK, and Agarwal; see Online Data Supplement Part 3, Table 3.10). The RR of CHF among blacks were 1.4 (95% CrI: 0.68–3.2) for ACEIs; 1.2 (95% CrI: 0.44–3.2) for beta blockers; and 1.4 (95% CrI: 0.60–2.8) for CCBs, compared with THZs (see Online Data Supplement Part 3, Figure 3.17). For stroke, there were 4 studies among blacks (ALLHAT, AASK, LIFE, and Agarwal; see Online Data Supplement Part 3, Table 3.11). The RR of stroke among blacks was 1.4 (95% CrI: 0.70–2.8) for ACEIs; 2.5 (95% CrI: 0.72–9.2) for ARBs; 1.2 (95% CrI: 0.48–3.0) for beta blockers; and 0.94 (95% CrI:

0.48–1.9) for CCBs, compared with THZs (see Online Data Supplement Part 3, Figure 3.18). For composite cardiovascular events, there were 4 studies among blacks (ALLHAT, AASK, LIFE, and Agarwal; see Online Data Supplement Part 3, Table 3.12). The RR of composite cardiovascular events among blacks were 1.2 (95% CrI: 0.64–2.2) for ACEIs; 1.42 (95% CrI: 0.52–4.6) for ARBs; 0.90 (95% CrI: 0.42–2.1) for beta blockers; and 1.0 (95% CrI: 0.52–1.8) for CCBs, compared with THZs (see Online Data Supplement Part 3, Figure 3.19). For renal events, there were only 2 studies among blacks (ALLHAT and AASK), and there were insufficient comparisons to calculate the analysis of heterogeneity.

At the request of the writing committee, we also examined effects by multiple subgroups of interest including age, race, sex, and diabetes mellitus status. Additional findings for each of the outcomes assessed (which are not discussed or referenced in the text) can be found in the Online Data Supplement Part 3 (Tables 3.13 through 3.65; and Figures 3.20 through 3.34). However, we found no significant effects—likely due to the relatively few studies for each class-to-class comparison with published data available for these analyses—thus these findings should be interpreted with caution.

Discussion: Part 3

In this meta-analysis, we found that no class of medications (i.e., ACEIs, ARBs, CCBs, or beta blockers) was significantly better than THZs as a first-line therapy for any outcome. THZs were associated with a significantly lower risk of stroke and cardiovascular events as compared to beta blockers and a lower risk of heart failure compared with CCBs. THZs also tended to be associated (that is, with credible intervals that excluded 0.95) with a lower risk of cardiovascular events and stroke compared with ACEIs, a lower risk of all-cause mortality and cardiovascular mortality compared with beta blockers, and a lower risk of cardiovascular events compared with CCBs. No significant differences were noted in analyses stratified by race, sex, age or diabetes mellitus status; however, given the relatively few numbers of studies and/or little overlap in comparison groups for all of the outcomes, these findings from subgroup analyses should be interpreted with caution. Our findings are generally consistent with prior meta-analyses (80,83,84). Network meta-analyses methods have been introduced relatively recently and provide many methodological advantages, compared with running individual meta-analyses for each class-to-class comparison. The network meta-analysis allowed us to make many comparisons of antihypertensive drug classes that were not studied in trials as direct head-to-head comparisons by generating a network of trials where each trial has at least 1 antihypertensive drug class in common with another. In doing so, the network meta-analysis incorporates all available evidence (strengthening the evidence base); allows the comparisons of antihypertensive drug classes with the same base comparator; consists of a simultaneous analysis of all treatments; and finally, it allows for more potential subgroup analysis. To our knowledge, only 1 publication, prior to this one, has used these methods (80). Consistent with our findings, this study by Psaty et al. (80) found that diuretics were associated with a lower risk of cardiovascular events and stroke compared with ACEIs. They also found that as compared to ACEIs, diuretics were associated with a 26% lower risk of heart failure. Although we found no significant association of THZs compared with ACEIs with heart failure, this may be attributable to differences in the number of studies included and the additional inclusion in this study of

more contemporary trials in which heart failure is more commonly assessed. For example, the previous findings included trials that compared antihypertensive medication classes to placebo controls, while in our study, we excluded placebo-controlled trials (80). This may be the reason why the Psaty et al. study demonstrated risk estimates of greater magnitude than we did; however, the direction of risk across class-to-class comparisons were generally the same. Consistent with the Psaty et al. study, we found that diuretics compared with beta blockers were associated with a lower risk of cardiovascular events. We additionally found that they were associated with a lower risk of cardiovascular mortality. When diuretics were compared with CCBs, they have been found to be consistently associated with a lower risk of heart failure. Although in contrast to the study by Psaty et al. (80), we found no association with cardiovascular events. Prior traditional meta-analyses have been relatively consistent with the findings from our network meta-analyses. One study found that diuretics were associated with a lower risk of heart failure and stroke, although this was borderline in overall results (37). Similar to our findings, CCBs have previously been found to be associated with higher risk of heart failure and beta blockers with a higher risk of stroke (37,83,85).

Understanding the benefits of one antihypertensive drug class versus another is of critical importance in determining which first-line medication should be recommended and informing clinical treatment decisions. Network meta-analytic methods allow us to incorporate direct and indirect evidence, thus using all available trial data to provide a valid estimate of the risks or benefits associated with one class of first-line medications versus another. Our findings support prior studies that have demonstrated a lower risk of many major cardiovascular events among individuals taking THZs versus other classes (80,83,84).

This systematic review has many strengths including a rigorous protocol that was strictly followed and use of sophisticated network meta-analytic methods that took advantage of all of the data available. However, there are some limitations that must be acknowledged. Our study only included published data. The trials we included had differences in study designs, specific drugs (within each class) being compared, and outcomes definitions.

In summary, we found that THZs were associated with a lower risk of many cardiovascular outcomes compared with other antihypertensive drug classes. This large and contemporary network meta-analysis supports prior findings that recommend THZs as the choice for first-line antihypertensive treatment among individuals with uncomplicated hypertension. Future studies should continue to examine whether these results are consistent across subgroups that vary by demographic or clinical characteristics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

APPENDIX

APPENDIX 1.

EVIDENCE REVIEW COMMITTEE RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—SYSTEMATIC REVIEW FOR THE 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA GUIDELINE FOR THE PREVENTION, DETECTION, EVALUATION, AND MANAGEMENT OF HIGH BLOOD PRESSURE IN ADULTS

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
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Suma Vupputuri	Kaiser Permanente Mid-Atlantic States—Research Scientist, Mid-Atlantic Permanente Research Institute	None	None	None	None	■ Sanofi, Inc. ^{‡*}	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% of the voting stock or share of the business entity, or ownership of \$5000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. According to the ACC/AHA, a person has a relevant relationship IF: a) the relationship or interest relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the document; or b) the company/entity (with whom the relationship exists) makes a drug, drug class, or device addressed in the document, or makes a competing drug or device addressed in the document; or c) the person or a member of the person's household, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document. Please refer to <http://www.acc.org/guidelines/about-guidelines-and-clinicaldocuments/relationships-with-industry-policy> for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

* Indicates significant relationship.

[‡] Dr. Vupputuri entered into a relationship as a subcontracted co-investigator on July 5, 2017 via the MidAtlantic Permanente Research Institute and the Center for Health Research at Kaiser Permanente Northwest, as part of a

retrospective cohort study funded by Sanofi, Inc. The contract itself was between the MidAtlantic Permanente Research Institute and the Center for Health Research at Kaiser Permanente Northwest. Although funding was processed via two research organizations, this was still considered to be “RWI” and is thus listed in the disclosure table. At this time, the ERC had already worked approximately three years, and all data gathering, analyses, and conclusions had already been formulated. Nevertheless, relevant analyses and sections of the ERC report were independently scientifically reviewed by David M. Reboussin, Norrina B. Allen, Daniel T. Lackland, Michael E. Griswold, Edgar (Pete) R. Miller III, Eliseo Guallar, Yuling Hong, and Angela M. Thompson-Paul, and this review and the finalized ERC report were then re-vetted and voted on for endorsement by the ERC and the hypertension guideline writing committee.

[‡]On March 1, 2018 (after publication of this Systematic Review), Dr. Polonsky, after having reviewed her listing on the CMS Open Payments Data website, realized that she had been a local PI in the STRENGTH trial, supported by AstraZeneca, and promptly reported this to the Task Force. Only 1 patient was recruited and Dr. Polonsky did not receive any direct salary support, but by ACC/AHA standards, this would constitute a relationship with industry (RWI) and thus, in the interest of full transparency, this footnote has been added.

AAPA indicates American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, indicates American College of Cardiology; ACPM, American College of Preventive Medicine; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; ERC, evidence review committee; NMA, National Medical Association; and PCNA, Preventive Cardiovascular Nurses Association.

APPENDIX 2.

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring	CKD = chronic kidney disease
ACEI = angiotensin-converting enzyme inhibitors	CrI = credible interval
ARB = angiotensin-receptor blockers	ERC = evidence review committee
BP = blood pressure	MI = myocardial infarction
CCB = calcium channel blockers	RCT = randomized controlled trial
CHF = congestive heart failure	RR = relative risk
CI = confidence interval	THZ = thiazide and thiazide-like diuretics

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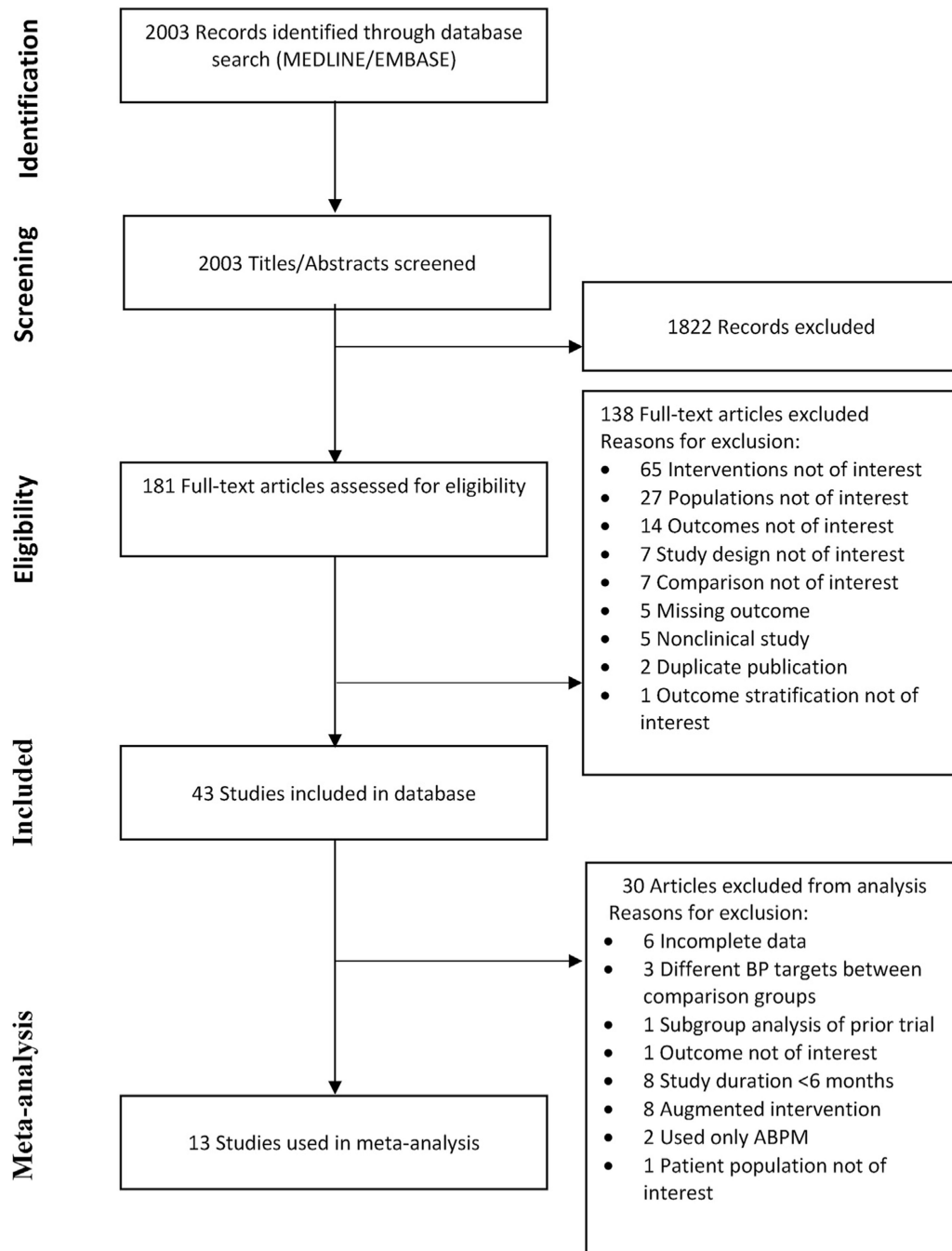


FIGURE 1. PRISMA Diagram of the Manuscripts Included in the Analyses
 ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; and PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

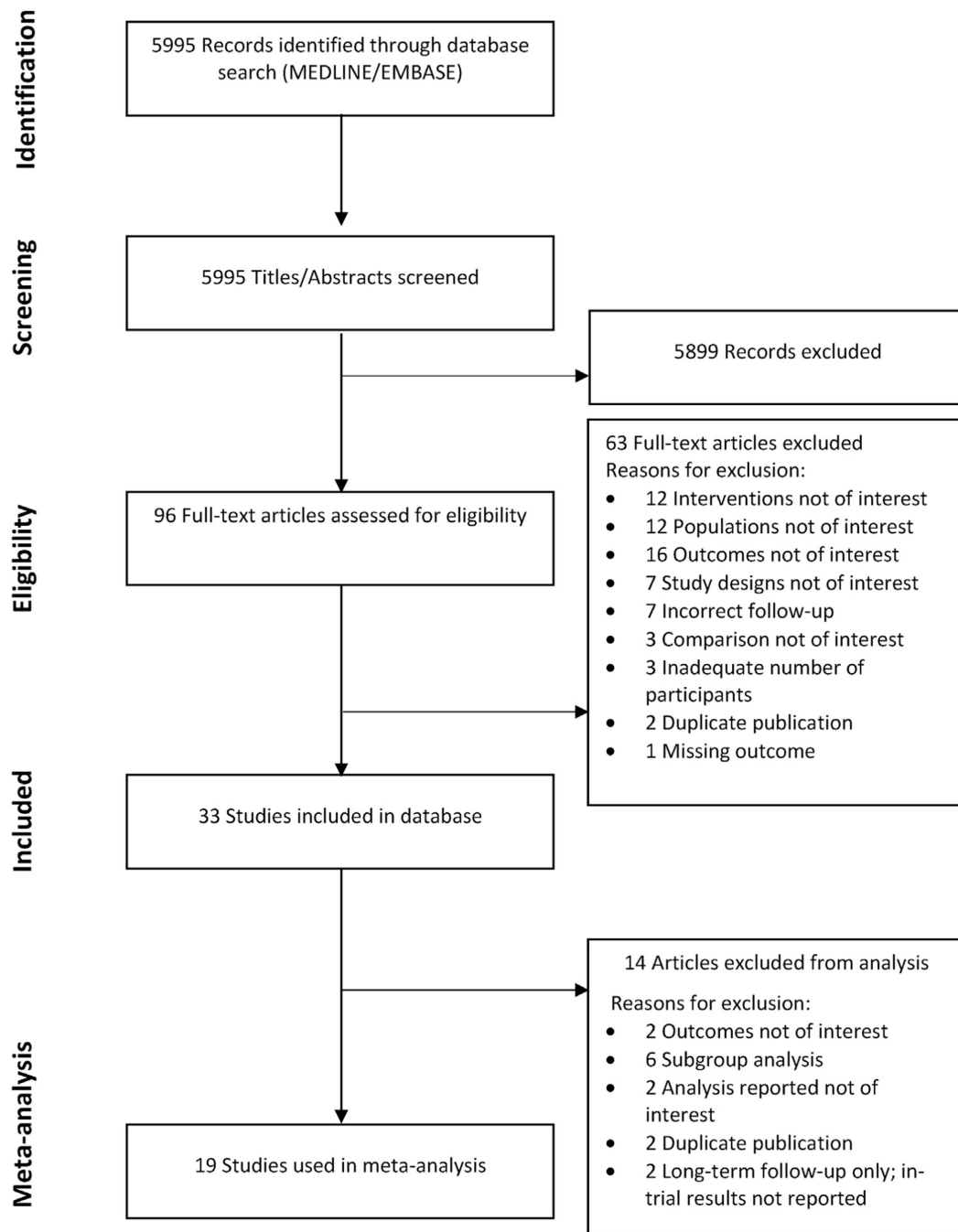


FIGURE 2.
PRISMA Diagram of the Manuscripts Included in the Analyses
PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

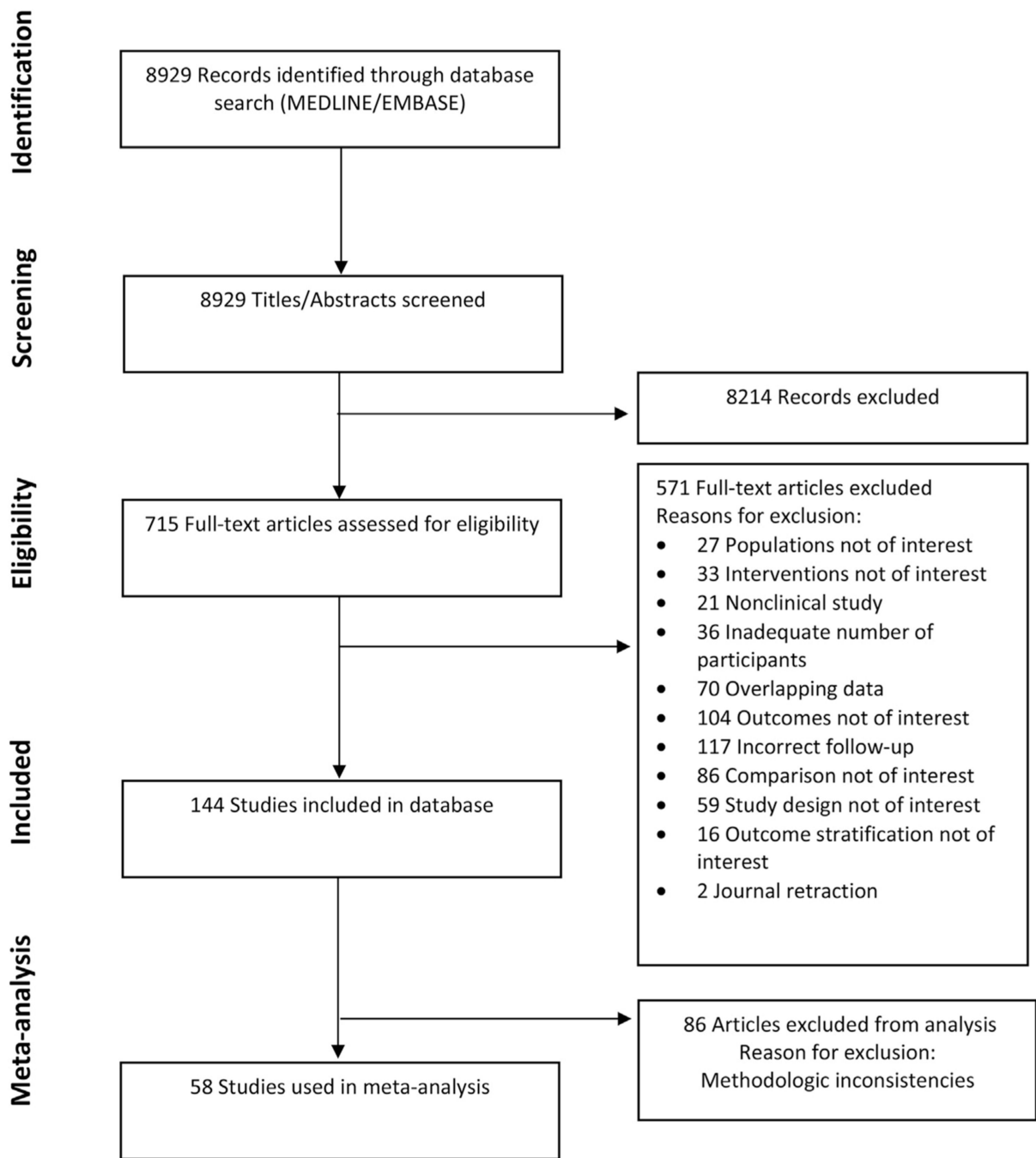


FIGURE 3.
 PRISMA Diagram of the Manuscripts Included in the Analyses
 PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.