HHS Public Access

Author manuscript

*Am J Prev Med*. Author manuscript; available in PMC 2018 March 05.

Published in final edited form as:

*Am J Prev Med*. 2017 December ; 53(6 Suppl 2): S131–S142. doi:10.1016/j.amepre.2017.06.020.

# Cost-effectiveness Analyses of Antihypertensive Medicines: A Systematic Review

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## Abstract

**Context—**Hypertension affects one third of the U.S. adult population. Although cost-effectiveness analyses of antihypertensive medicines have been published, a comprehensive systematic review across medicine classes is not available.

**Evidence acquisition—**PubMed, Embase, Cochrane Library, and Health Technology Assessment were searched to identify original cost-effectiveness analyses published from 1990 through August 2016. Results were summarized by medicine class: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), thiazide-type diuretics, β-blockers, and others. Incremental cost-effectiveness ratios (ICERs) were adjusted to 2015 U.S. dollars.

**Evidence synthesis—**Among 76 studies reviewed, 14 compared medicines with no treatment, 16 compared medicines with conventional therapy, 29 compared between medicine classes, 13 compared within medicine class, and 11 compared combination therapies. All antihypertensives were cost effective compared with no treatment (ICER/quality-adjusted life year [QALY]=dominant–$19,945). ARBs were more cost effective than CCBs (ICER/QALY=dominant–$13,016) in nine comparisons, whereas CCBs were more cost effective than ARBs (ICER/QALY=dominant) in two comparisons. ARBs were more cost effective than ACEIs (ICER/QALY=dominant–$34,244) and β-blockers (ICER/QALY=$1,498–$18,137) in all eight comparisons.

**Conclusions—**All antihypertensives were cost effective compared with no treatment. ARBs appeared to be more cost effective than CCBs, ACEIs, and β-blockers. However, these latter findings should be interpreted with caution because these findings are not robust due to the substantial variability across the studies, including study settings and analytic models, changes in the cost of generic medicines, and publication bias.



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SUPPLEMENTAL MATERIAL

Supplemental material associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2017.06.020.

## CONTEXT

Hypertension is associated with a high economic burden at the individual and population levels. It is one of the most common primary diagnoses in the U.S., affecting one third of the adult population.[1] In the U.S., the annual estimated direct and indirect costs of hypertension were $47.3 billion and $3.9 billion, respectively (annual average 2012–2013).[2] The annual costs for patients treated for hypertension averaged $733 per adult in 2010.[3] In addition, hypertension is an independent risk factor for other costly diseases. Antihypertensive therapy reduces the incidence of stroke (35%–40%), myocardial infarction (20%–25%), and heart failure (>50%).[4] Prescription medicine costs account for about half of the total medical costs for the treatment of hypertension.[3,5,6]

Many pharmacologic treatment options are available for the management of hypertension. The following medicine classes are commonly used[7]: Angiotensin-converting enzyme inhibitors (ACEIs) inhibit the formation of angiotensin II, which is a vasoconstrictor. Angiotensin II receptor blockers (ARBs) block the binding of angiotensin II to receptors on blood vessels, leading to vasodilation. Calcium channel blockers (CCBs) decrease vascular resistance by vascular smooth muscle relaxation. Diuretics are divided into three groups: thiazide-type or thiazide-like diuretics (TDs), loop diuretics, and potassium-sparing diuretics. TDs are the most commonly used diuretics,[8] and work by blocking sodium chloride reabsorption at the distal convoluted tubule cells in the kidneys. β-blockers inhibit activation by directly suppressing renin release and also block the effects of circulating catecholamines and reduce heart rate and cardiac output.

The 2014 evidence-based guideline for the management of high blood pressure in adults[9] recommends several possible medicine classes for initial treatment of hypertension. TD, CCB, ACEI, or ARB classes are recommended as the initial choice of antihypertensive medicines for non–African-American patients and for patients with diabetes. For African-American patients TDs and CCBs are recommended, and for patients with chronic kidney disease, ACEIs and ARBs are recommended. Prescribers may consider adding another medicine from TD, CCB, ACEI, or ARB classes for the second step, and then β-blockers, aldosterone antagonists, or others for the third step. Similarly, several medicine classes are recommended for first-line therapy in the National Institute for Health and Care Excellence guideline for hypertension.[10] The recommended initial treatment option is ACEIs or low-cost ARBs for patients aged <55 years, CCBs for those aged ≥55 years or African American, and TD if CCBs are not suitable; β-blockers are not a preferred initial therapy. The second-line therapy is dual therapy of ACEs or ARBs with a CCB for most patients. The third-line therapy is the use of three medicines, including ACE or ARB with a CCB, and a TD, if required. Because several pharmacologic treatment options can be used for the first-line therapy, it is important to evaluate which medicines are more cost effective among those options.

The evidence from pharmacoeconomic evaluations can provide valuable information for decision makers in setting public health priorities. Many pharmacoeconomic studies of antihypertensive medicines conducted in recent years have found control of hypertension to be cost effective. Several systematic reviews of these studies also have been published, but

their focus has been on a specific medicine, such as irbesartan,[11] or medicine class, such as ACEIs or ARBs.[12] Thus, no comprehensive review has been conducted for studies across all anti-hypertensive medicine classes. The objectives are to systematically review all pharmacoeconomic evaluations of antihypertensive medicines and summarize the cost effectiveness of these medicines.

## EVIDENCE ACQUISITION

### Search Strategy

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The authors performed a literature search using PubMed, Embase, Cochrane Library, and Health Technology Assessment from January 1, 1990 through August 31, 2016. The search terms were a combination of study type (*health economics* OR *pharmacoeconomics* OR *economic burden* OR *cost analysis* OR *economic analysis* OR *cost-effectiveness* OR *cost-utility* OR *cost-benefit*) and study intervention or outcomes (*hypertension* OR *high blood pressure* OR *antihypertensive*). All references were manually checked for the review articles retrieved.

### Eligibility Criteria

Pharmacoeconomic studies were included if: (1) the study population was being treated for hypertension; (2) antihypertensive medicines were used to treat hypertension; (3) both costs and outcomes were assessed; (4) outcomes were reported as natural unit (e.g., life year [LY], blood pressure reduction, cardiovascular event avoided), utility unit (quality-adjusted life year [QALY]), or monetary unit; and (5) full-text articles were published in English. Studies were excluded if they did not describe specific antihypertensive medicines and compared medicine adherence, medicine price, single-pill fixed-dose combination therapy, and administration times.

### Data Extraction

Studies that met eligibility criteria were categorized by five comparison types: (1) medicines versus placebo or no treatment; (2) medicines versus conventional therapy or standard of care that was defined as a situation where patients used any medicines that they had used before clinical trials except intervention medicines, but authors did not describe the names of medicines; (3) medicines between different medicine classes; (4) medicines within the same medicine class; and (5) different combination therapies. The cost-effectiveness evidence of medicines was summarized by medicine class: ACEIs, ARBs, CCBs, TDs, β-blockers, and others. The following information was summarized for each study: country where the study was conducted, medical conditions of study population, kind of economic evaluation methods, perspective, study framework, time horizon, sensitivity analyses, treatment type, outcomes, funding source, and cost-effectiveness evidence (e.g., incremental cost-effectiveness ratio [ICER]). Two reviewers screened studies according to the eligibility criteria, and differences were resolved by consensus between the reviewers. The cost estimates of the studies were adjusted to 2015 U.S. dollars using the Personal Consumption Expenditures by Health Function.[14] For studies reporting costs in other currencies, the

Purchasing Power Parity Index was used to convert the estimates to U.S. dollars in the same year and then adjusted for inflation.[15]

### Quality Assessment

The quality of the pharmacoeconomic studies was assessed by the 100-point Quality of Health Economic Studies scale with all 16 items.[16]

## EVIDENCE SYNTHESIS

### Study Characteristics

Figure 1 is a flow diagram of the review process based on the PRISMA guideline. A total of 3,247 potentially relevant articles were identified. After excluding duplication, the abstracts of 2,718 articles were screened and 1,885 were excluded. Then the full text of 833 articles was screened to assess eligibility based on the inclusion criteria. Through this process, 99 articles were identified as pharmacoeconomic studies of antihypertensive medicines. An additional 23 studies were excluded for not meeting the inclusion criteria, and the remaining 76 studies were grouped into (1) studies that compared antihypertensive medicines with no treatment ($n$=14), (2) studies that compared antihypertensive medicines with conventional therapy ($n$=16), (3) studies that compared medicines between medicine classes ($n$=28), (4) studies that compared medicines within medicine class ($n$=13), and (5) studies that compared different combination therapies ($n$=11). Six studies were included in two groups.

Table 1 shows the characteristics of pharmacoeconomic studies of antihypertensive medicines. Most studies were conducted in Europe ($n$=41), followed by North America ($n$=16). About half of the study populations were patients with hypertension alone ($n$=39), and another half were patients with hypertension and comorbidities ($n$=37). Cost-effectiveness analysis and cost-utility analysis were used frequently ($n$=56 and $n$=31, respectively). The perspectives of health care and third-party payer were used frequently. Among 64 studies that reported funding source for research, 80% ($n$=51) received partial or full support from private industry.

Figure 2 shows the frequencies of antihypertensive medicines analyzed in the literature. Thirty-six medicines were assessed. ARBs were the most frequently evaluated and were assessed 62 times as either interventions or comparators in 42 studies. The most frequently included ARBs were losartan ($n$=20) and irbesartan ($n$=15). CCBs were assessed 32 times ($n$=31) and amlodipine was the most commonly used medicine in this class ($n$=19). Cost effectiveness of ACEIs was assessed 28 times ($n$=28). β-blockers were included 25 times ($n$=23) and atenolol was the most common medicine in this class ($n$=16). Cost effectiveness of TDs was evaluated 17 times ($n$=17) and hydrochlorothiazide (HCTZ) was the most frequently used medicine in this class ($n$=10). The mean Quality of Health Economic Studies score was 82.5 points (SD=13.8 points). Appendix Table 1 (available online) describes the results of quality assessment in the literature based on the Quality of Health Economic Studies instrument.

## Cost-Effectiveness Evidence

Table 2A shows the summary of cost effectiveness of antihypertensive medicines compared with no treatment and conventional treatment. In 14 studies, all types of medicines were cost effective compared with placebo/no treatment (25 comparisons). Of these 14 studies, hypertension was defined by systolic blood pressure in five studies: ≥160 mmHg for two studies, ≥150 mmHg for one study, and ≥140 mmHg for two studies. ACEIs and TDs were frequently evaluated medicines (ten comparisons for both) and ARBs and β-blockers were also assessed (four comparisons and one comparison, respectively). The ICER ranges were from dominant to $19,945 for QALY and from dominant to $13,856 for LY. The least cost-effective scenario for QALY was the mono-therapy of HCTZ, and that for LY was the combination therapy of perindopril and indapamide. Appendix Table 2 (available online) summarizes each article on the comparisons between antihypertensive medicines and no treatment.

For 16 studies, the control group was treated with conventional therapy, which was mostly defined as using control hypertensive medicines (e.g., β-blockers, TDs, and other classes) except intervention hypertensive medicines (e.g., ACEIs, ARBs, and CCBs) without the specification of medicine name. All types of medicines were more cost effective than conventional treatment (16 comparisons), except one comparison that amlodipine was less cost effective. The most frequent evaluations were ARBs (13 comparisons) and ACEIs and CCBs were also assessed (two comparisons for each). Except for amlodipine, the ICER ranged from dominant to $29,331 for QALY, and the least cost-effective scenario for QALY was the use of irbesartan. Intervention medicines were a dominant option for LY compared with conventional treatment. Appendix Table 3 (available online) provides the summary of each article on the comparisons between intervention antihypertensive medicines and conventional treatment used in this review.

Table 2B summarizes the cost effectiveness of antihypertensive medicines from different medicine classes. The cost effectiveness of ARBs was most frequently assessed. First, nine of 11 comparisons between ARBs and CCBs concluded that ARBs were more cost effective than CCBs. Eprosartan, irbesartan, losartan, and valsartan were cost effective compared with amlodipine, and eprosartan was cost effective compared with nitrendipine (ICER/QALY=dominant–$10,016, ICER/LY=dominant); whereas CCBs (amlodipine) were more cost effective than ARBs (valsartan) in two comparisons. Second, all studies concluded that ARBs were more cost effective than ACEIs and β-blockers. Regarding ACEIs, eprosartan was more cost effective than enalapril and perindopril, and losartan was more cost effective than fosinopril (three comparisons; ICER/QALY=dominant–$34,244, ICER/LY=dominant). Regarding β-blockers, losartan was more cost effective than atenolol (five comparisons; ICER/QALY=$1,498–$18,137, ICER/LY=dominant–$13,603). Third, only one comparison between ARBs and TDs was evaluated, which found that chlorthalidone was more cost effective than losartan (ICER not reported).

In three comparisons between CCBs and ACEIs, CCBs were the more cost-effective option. Nifedipine was more cost effective than lisinopril or captopril, and amlodipine was more cost effective than enalapril (ICER not reported). When comparing CCBs with β-blockers, the results were inconsistent. Nifedipine was more cost effective than propranolol in one

comparison (ICER not reported), whereas propranolol was more cost effective than nifedipine in one comparison (ICER not reported). In the comparison between CCBs and TDs, amlodipine was more cost effective than chlorthalidone (one comparison; ICER/QALY=$53,594, ICER/LY=$62,202), whereas HCTZ and chlorthalidone were more cost effective than nifedipine and amlodipine (two comparisons; ICER not reported). TDs were more cost effective than ACEIs in five comparisons (ICER/QALY=dominant, ICER/LY=dominant, HCTZ vs lisinoril, enalapril, or captopril, and chlorthalidone vs lisinoril and enalapril), whereas ACEIs were more cost effective than TDs in only one study (ICER/QALY=$19,474, enalapril vs HCTZ).

ARBs were more cost effective than CCBs in hypertensive patients with diabetes or renal disease, or both, in all comparisons. Specifically, irbesartan and valsartan were more cost effective than amlodipine in patients with diabetes mellitus (five comparisons and one comparison, respectively; ICER/QALY=dominant, ICER/LY=dominant) and renal disease (six comparisons; ICER/QALY=dominant, ICER/LY=dominant). ARBs were more cost effective than β-blockers in hypertensive patients with left ventricular hypertrophy in all comparisons. Specifically, losartan was more cost effective than atenolol (four comparisons; ICER/QALY=$1,498–$18,137, ICER/LY=dominant–$13,603). Appendix Table 4 (available online) summarizes the articles on the comparisons of antihypertensive medicines between different medicine classes.

Table 2C summarizes 13 studies about the cost effectiveness of antihypertensive medicines within the same medicine class for ARBs, β-blockers, and CCBs. ARBs were the most frequently evaluated class; ten studies made 19 comparisons. Overall, olmesartan, irbesartan, candesartan, and telmisartan were more cost effective than losartan and valsartan. Olmesartan, irbesartan, candesartan, telmisartan, and valsartan were more cost effective than losartan (eight comparisons; ICER/QALY=dominant–$33,567, ICER/LY=dominant–$28,326), whereas losartan was more cost effective than candesartan in one comparison. Olmesartan, irbesartan, candesartan, and telmisartan were more cost effective than valsartan (six comparisons; ICER/QALY=dominant–$34,678, ICER/LY=$10,275–$27,006). Appendix Table 5 (available online) provides the summary of each study on the comparisons of antihypertensive medicines within the medicine classes.

Eleven studies compared the cost effectiveness of different types of combination therapies. In two studies, amlodipine-based treatment with perindopril as an adjunct treatment was more cost effective than atenolol-based treatment with bendroflumethiazide as an adjunct treatment (ICER/QALY=$5,649–$31,975, ICER/LY=$20,495–$31,165). Dual therapies were more cost effective than monotherapy and triple therapy. A dual therapy of azelnidipine and olmesartan was more cost effective than a monotherapy with either azelnidipine or olmesartan (ICER/QALY=dominant). A dual therapy of candesartan (low dose) and nifedipine was also more cost effective than a monotherapy with candesartan or nifedipine (ICER/blood pressure reduction=dominant). However, a triple therapy of bendrofluazide, atenolol, and enalapril was less cost effective than a dual therapy of bendrofluazide and atenolol (ICER=not reported). Appendix Table 6 (available online) summarizes the articles on the comparisons among different types of combination therapies.

# DISCUSSION

## Cost-Effectiveness Evidence

As expected, this review found that treating hypertension with medicines was consistently more cost effective than not treating it, thanks to the remarkable progress in the treatment of hypertension in recent decades. ARBs were found to be more cost effective than CCBs in nine comparisons, whereas CCBs appeared to be more cost effective than ARBs in two comparisons. ARBs were more cost effective than ACEIs and β-blockers in all eight comparisons. Within ARBs, losartan was a less cost effective medicine in eight comparisons. These findings are less robust because of the heterogeneity of study setting and analytic methods and changes in the cost of generic medications.

A previous study found that approximately one half of U.S. adults with hypertension did not have their hypertension controlled. Of those who were uncontrolled: 33.1% were unaware; 20.3% were aware, but uncontrolled; and 46.6% were aware, treated, and uncontrolled.[17] When considering the economic benefit of treating hypertension, more effort should be required to identify people who are not aware of their hypertension and to treat those who are not receiving treatment despite being aware of their hypertension.

Pharmacoeconomic evaluations of medicines are usually conducted for newly marketed medicines. ARBs are the newest class of antihypertensive medicine. In 1995, the first ARB, losartan, was approved by the U.S. Food and Drug Administration, followed by valsartan in 1996. Irbesartan, eprosartan, candesartan, telmisartan, and olmesartan were approved between 1997 and 2002.[18] Thus, ARBs were the most frequently evaluated—in 42 of 76 studies in this review, mostly published between 2000 and 2009. The studies reviewed found that ARBs were a more cost-effective option than medicines in the CCB, ACEI, or β-blocker classes. Furthermore, losartan and valsartan, the first U.S. Food and Drug Administration – approved ARBs, were less favorable options among ARBs. Thus, more frequent evaluations of ARBs may lead to better cost-effectiveness results for this medicine class, especially for more recently marketed ARBs than losartan and valsartan.

This review found that ARBs were more cost effective than CCBs in hypertensive patients with diabetes and renal disease (irbesartan and valsartan versus amlodipine) and β-blockers in patients with left ventricular hypertrophy (losartan versus atenolol). According to the new evidence-based guideline for the management of high blood pressure,[9] TDs, CCBs, ACEIs, and ARBs are recommended as the initial choice for patients with diabetes, and ACEIs and ARBs are recommended for patients with chronic kidney disease. The findings of this review could be useful for choosing appropriate anti-hypertensive medicines for patients with diabetes, renal disease, or left ventricular hypertrophy.

## Study Design and Quality

When assessing study quality, study perspective, the source of input parameters, time horizons, and outcome measures must be considered. Societal perspective is the gold standard of pharmacoeconomic studies because it incorporates all costs and health outcomes, although other perspectives may be better for some decision-making situations.

[19,20] However, only a few studies in this review used a societal perspective. The majority stated that they considered a payer perspective (e.g., third-party payer perspective).

Second, efficacy refers to outcomes under ideal circumstances, whereas effectiveness refers to outcomes under real-world settings.[21,22] Although efficacy and effectiveness lie on a continuum, the source of input parameters of pharmacoeconomic studies from clinical trials have higher internal validity, whereas those from observation studies have higher external validity. About one third of the studies combined efficacy data from clinical trials using a Markov model, and another third evaluated efficacy data from clinical trials by using regression-type analyses. Thus, the source of input parameters came from clinical trials in the majority of the included studies.

Third, more than half of the studies adopted a time horizon of less than 10 years, even though hypertension is a chronic disease. Although medicine dosages might be able to be reduced after patients achieve normal blood pressure and maximize healthy lifestyle behaviors beneficial for hypertension control (maintaining a normal weight, being physically active, and consuming a low sodium diet) and maintain it for a year or more, the use of antihypertensive medicines is often not able to be stopped. Treatment frequently should be continued over a lifetime.[23] When considering the natural course of hypertension, a long time horizon is preferred for pharmacoeconomic studies.

Finally, a number of outcomes were evaluated in the studies. Primary clinical outcomes were commonly used. The most common outcome was LYs, followed by QALYs. Other intermediate clinical outcomes were blood pressure reduction and avoiding cardiovascular disease events, end-stage renal disease, or dialysis. QALYs has been considered a more important measure of effectiveness in pharmacoeconomic evaluation than LYs.[24,25] However, only about 40% of the included studies used QALYs as an effectiveness measure in this review.

This study has several strengths. First, this review is the first comprehensive synthesis of the evidence of cost effectiveness for antihypertensive medicines to the authors' knowledge, and it presents detailed cost-effectiveness information. Second, this review included the majority of the published cost-effectiveness studies of antihypertensive medicines and adjusted all cost-related values from different time and settings to 2015 U.S. dollars for better comparison. Finally, this review also assessed quality of the literature and pointed out the weaknesses of the literature. Because the findings from the literature were similar across low- and high-quality literature, this review included all 76 studies. In addition, identifying the weaknesses of the current literature will help future cost-effectiveness analyses of antihypertensive medicines.

## Limitations

This study also has several limitations. First, only English language peer-reviewed publications were included. Thus, other important pharmacoeconomic studies of antihypertensive medicines published in non-English language peer-reviewed journals may have been missed. Second, the availability of generic medicines changes over time. Although it is well known that substituting generic medicines for brand-name medicines

lowers costs,[26] it is important to acknowledge the impact of including pharmacoeconomic studies that do not specify the cost—based on generic or brand formulations or both —on a cost-effectiveness analysis. For example, since losartan became available as a generic in 2010,[27] the results of studies evaluating the cost effectiveness of losartan prior to 2010 cannot be generalized with the results of studies conducted after 2010. The same is true for all other ARBs cost-effectiveness studies where the cost of the formulation (i.e., generic versus brand) was not specified. In this analysis, most studies did not clarify if the cost of medicines were based on the brand or generic formulation. For this reason, the cost-effectiveness calculations reported in this report may be imperfect, and the usefulness of the results limited. Finally, cost-effectiveness evidence may depend on the blood pressure level, race/ethnicity, age, or comorbidity status of the patients. However, many studies in the literature did not provide this specific information; thus, cost-effectiveness evidence for specific population groups could not be derived.

These findings should be interpreted with caution for several reasons. First, potential conflicts of interest for authors of industry-sponsored studies may have influenced the way they develop models and gathered input information for analytic models. A systematic review on bias in published cost-effectiveness studies demonstrated that studies sponsored by industry were associated with a favorable cost-effectiveness ratio compared with studies sponsored by non-industry sources, although there was no difference in the quality of the research.[28,29] In this review, 64 studies reported a funding source for research, 51 (80%) of them financially supported by industry. These studies provided positive evidence for the companies that sponsored them. As such, there is a possibility of publication bias of the results in this review. Another reason is a substantial variability across studies. For example, study settings varied across countries because of differences in financial and healthcare systems,[30,31] and drug prices often differ widely because of bargaining power.[32] Many studies were conducted in Europe. This may be due to the fact that European governments often emphasize cost-effectiveness evidence in their healthcare system. In addition, the definitions and measurements of outcomes and analytical approaches in each study also varied across study settings and methodologies. Although studies were categorized into five groups, there were still substantial variabilities across studies within groups. As such, the Appendix Tables 1–6 (available online) are provided to summarize each study. Finally, although cost effectiveness of antihypertensive medicines could be an aid for clinical decisions, the availability of generic medicines might make the published cost-effectiveness information less valid.

Several research gaps were identified in the literature. First, no study assessed the cost effectiveness of medicines according to race/ethnicity in the U.S. Because race/ethnicity is a key factor when determining appropriate treatment options, future studies could evaluate the cost effectiveness of antihypertensive medicines by race/ethnicity. Second, more research is needed on the cost effectiveness of antihypertensive medicines by patient blood pressure level, because using hypertensive medicines may be less cost effective in patients with mild hypertension compared with moderate or severe hypertension. Third, more evaluations should be conducted on different types of combination therapies. This review found 11 studies that compared different types of combination therapies. However, considering many hypertensive adults take multiple medications concurrently, research should be conducted to

identify optimal number of medications or types of combination by their characteristics. Finally, developing a standard to measure effectiveness in hypertension should be considered, especially in adults with other comorbidities, such as diabetes and renal disease.

## CONCLUSIONS

The treatment of hypertension using antihypertensive medicines is cost effective compared with no treatment. Among medicine classes, ARBs appear to be more cost effective than CCB, ACEI, and β-blocker classes. However, these results should be interpreted with caution because of potential publication bias (i.e., funding bias) and the heterogeneity of study setting.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

Publication of this article was supported by the U.S. Centers for Disease Control and Prevention (CDC), an Agency of the U.S. Department of Health and Human Services, and the Association for Prevention Teaching and Research (APTR) Cooperative Agreement No. 1U36 OE000005.

The findings and conclusions in this publication are those of the authors and do not necessarily represent the official position of the CDC.

No financial disclosures were reported by the authors of this paper.

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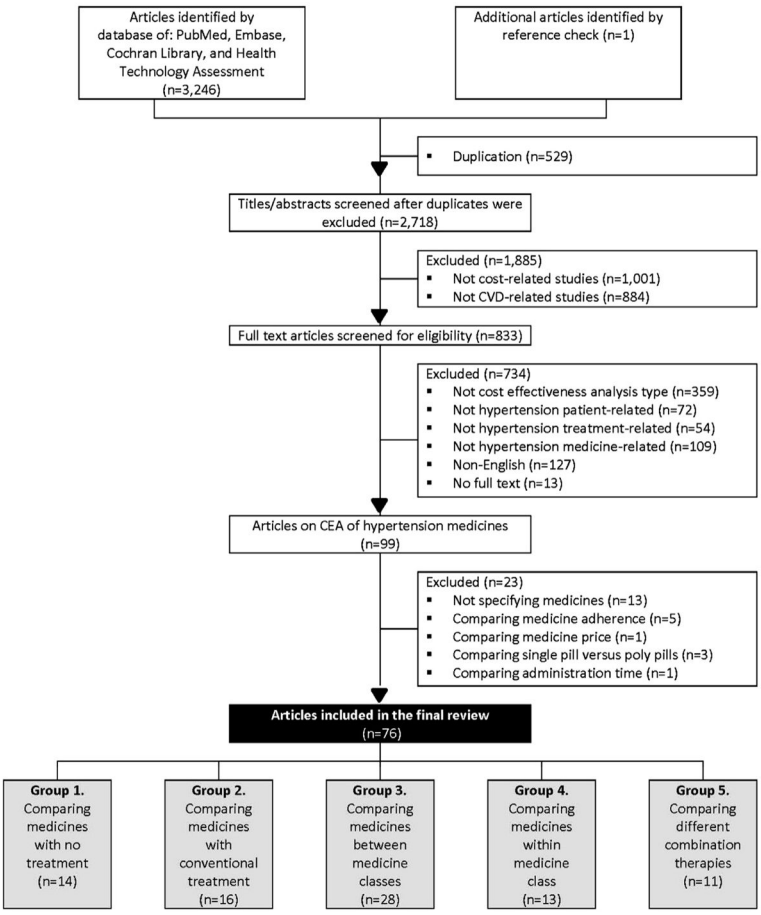


**Figure 1.**

Article identification and selection process of CEAs of antihypertensive medicines published in 1990–2016.

*Note:* The sum of the number of articles in the five groups was > 76 because six studies were included in multiple groups.

CEA, cost-effectiveness analysis; CVD, cardiovascular disease.

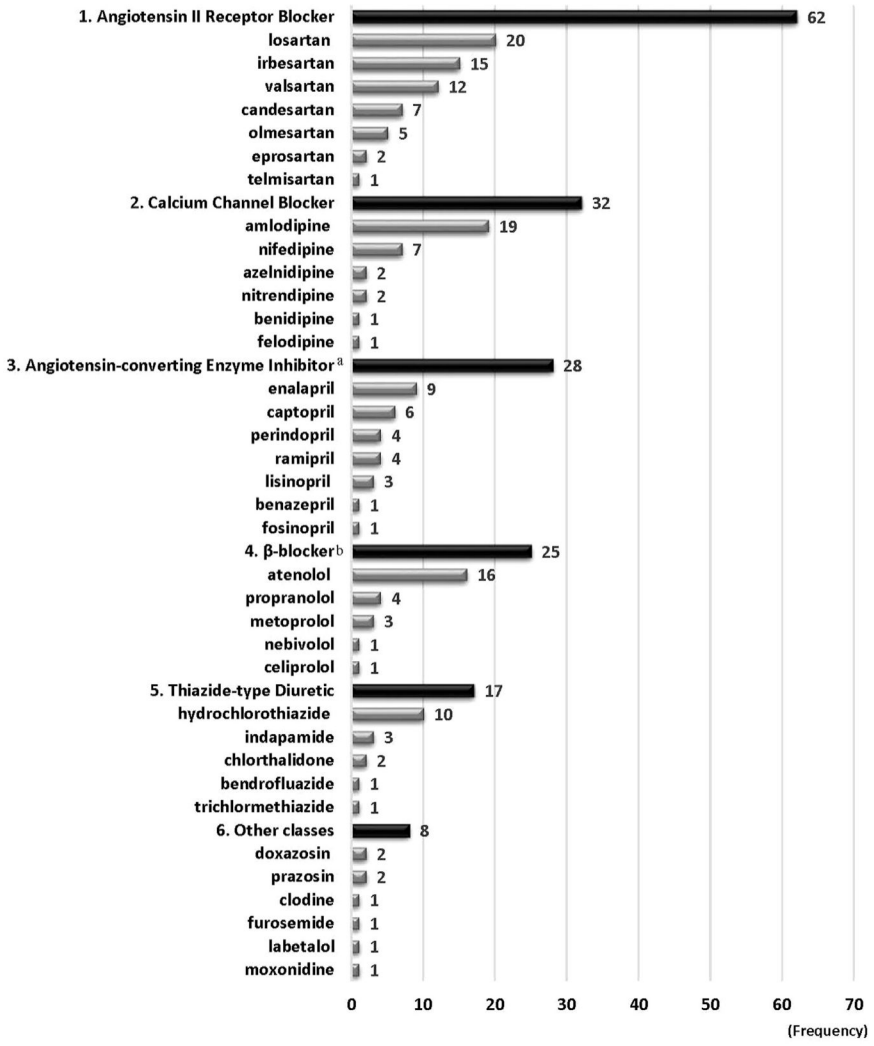


**Figure 2.**

Frequencies of antihypertensive medicines by medicine classes in cost-effectiveness analyses published in 1990–2016 ($n$=76).

*Note:* Medicines were excluded for counting if they were used as adjunctive therapy for both intervention and control groups or as needed. All calcium channel blockers were dihydropyridine calcium channel blockers. All β-blockers were β1-selective β-blockers except propranolol, which is non-selective.

**Table 1**

Characteristics and Quality of Cost-Effectiveness Analyses of Antihypertensive Medicines Published in 1990–2016 ($n$=76)

| Characteristics | Number of studies |
|---|---|
| Location | |
| Europe | 41 |
| North America (U.S. and Canada) | 16 |
| Others | 19 |
| Medical conditions of study population | |
| HTN | 39 |
| HTN+diabetes+renal disease | 12 |
| HTN+diabetes | 9 |
| HTN+renal failure | 4 |
| HTN+cardiovascular disease | 9 |
| HTN+cerebrovascular disease | 3 |
| Economic evaluation type | |
| Cost-minimization analysis | 1 |
| Cost-effectiveness analysis | 42 |
| Cost-utility analysis | 17 |
| Cost-benefit analysis | 2 |
| Cost-effectiveness and utility analysis | 14 |
| Perspective[a] | |
| Health care | 30 |
| Third-party payer | 19 |
| Not specified payer | 8 |
| Societal | 7 |
| Others | 4 |
| Not reported | 10 |
| Study framework | |
| Trial-based | 28 |
| Model-based | 24 |
| Trial- and model-based | 24 |
| Time horizon[b] | |
| ≤1 year | 13 |
| >1 year and ≤10 years | 38 |
| >10 years | 35 |
| Not reported | 3 |
| Sensitivity analysis | |
| Conducted | 64 |

| Characteristics | Number of studies |
|---|---|
| Not conducted | 12 |
| Treatment type | |
| Monotherapy | 35 |
| Combination therapy | 14 |
| Monotherapy and/or combination therapy | 27 |
| Outcomes[c] | |
| QALY | 31 |
| LY | 37 |
| Blood pressure reduction | 8 |
| Cardiovascular disease-related | 4 |
| Renal disease-related | 7 |
| Monetary | 2 |
| Others | 6 |
| Funding source | |
| Private industry | 46 |
| Nonprofit organization | 8 |
| Private industry+nonprofit organization | 5 |
| None | 5 |
| Not reported | 12 |
| Quality assessment score[d] | |
| >90 | 21 |
| 81–90 | 33 |
| 71–80 | 12 |
| ≤70 | 10 |

[a]Two studies took two perspectives.

[b]Eleven studies used more than two time horizons.

[c]Seventeen studies assessed more than two outcomes.

[d]The mean Quality of Health Economic Studies score was 82.5 (SD=13.8).

HTN, hypertension; LY, life year; QALY, quality-adjusted life year.

## Table 2A

Summary of Cost Effectiveness of Antihypertensive Medicines From the Literature Published in 1990–2016: Intervention Treatment Versus No Treatment and Intervention Treatment Versus Conventional Treatment (*n*=30)

| | Controls | |
|---|---|---|
| **Interventions** | **No treatment** | **Conventional treatment** |
| ARB preferred | | |
| Comparison, *n* | 4 | 13 |
| ICER | QALY: dominant–$10,976<br>LY: $7,594 | QALY: dominant–$29,331<br>LY: dominant |
| Medicines assessed | Valsartan, irbesartan, losartan | Irbesartan, losartan, candesartan |
| CCB preferred[a] | | |
| Comparison, *n* | 0 | 1 |
| ICER | | NR |
| Medicines assessed | | Amlodipine |
| ACEI preferred | | |
| Comparison, *n* | 10 | 2 |
| ICER | QALY: dominant–$17,851<br>LY: dominant–$13,856 | NR |
| Medicines assessed | Lisinopril, perindopril, ramipril, benazepril, enalapril, captopril, perindopril +indapamide | Ramipril, captopril |
| β-blocker preferred | | |
| Comparison, *n* | 1 | 0 |
| ICER | QALY: dominant | |
| Medicines assessed | Labetalol | |
| TD preferred | | |
| Comparison, *n* | 10 | 0 |
| ICER | QALY: $4,987–$19,945<br>LY: dominant–$13,856 | |
| Medicines assessed | HCTZ, indapamide, perindopril+indapamide | |

[a]In one comparison, amlodipine is less cost-effective than conventional therapy.

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HCTZ, hydrochlorothiazide; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life year; TD, thiazide-type diuretic.

## Table 2B

Summary of Cost Effectiveness of Antihypertensive Medicines From the Literature Published in 1990–2016: Comparison Between Medicine Classes (*n*=28)

| | Controls | | | | |
|---|---|---|---|---|---|
| **Interventions** | **ARB** | **CCB** | **ACEI** | **β-blocker** | **TD** |
| ARB preferred | | | | | |
| Comparison, *n* | — | 9 | 3 | 5 | 0 |
| ICER | | QALY: dominant–$13,016<br>LY: dominant | QALY: dominant–$34,244<br>LY: dominant | QALY: $1,498–$18,137<br>LY: dominant–$13,603 | |
| Medicines assessed | | Eprosartan vs amlodipine; eprosartan vs nitrendipine; irbesartan vs amlodipine; losartan vs amlodipine; valsartan vs amlodipine | Eprosartan vs enalpril; eprosartan vs perindopril; losartan vs fosinopril | Losartan vs atenolol | |
| CCB preferred | | | | | |
| Comparison, *n* | 2 | — | 3 | 1 | 1 |
| ICER | QALY: dominant | | NR | NR | QALY: $53,594<br>LY: $62,202 |
| Medicines assessed | Amlodipine vs valsartan | | Nifedipine vs lisinopril; amlodipine vs enalapril; nifedipine vs captopril | Nifedipine vs propronolol | Amlodipine vs CTD |
| ACEI preferred | | | | | |
| Comparison, *n* | 0 | 0 | — | 1 | 1 |
| ICER | | | | NR | QALY: $19,457 |
| Medicines assessed | | | | Amlodipine vs atenolol | Enalapril vs HCTZ |
| β-blocker preferred | | | | | |
| Comparison, *n* | 0 | 1 | 1 | — | 2 |
| ICER | | NR | NR | | LY: $4,748 |
| Medicines assessed | | Propranolol vs nifedipine | Atenolol vs enalpril | | Metoprolol vs HCTZ; Propranolol vs HCTZ |
| TD preferred | | | | | |
| Comparison, *n* | 1 | 2 | 5 | 2 | — |
| ICER | NR | NR | QALY: dominant<br>LY: dominant | NR | |

| | Controls | | | | |
|---|---|---|---|---|---|
| **Interventions** | **ARB** | **CCB** | **ACEI** | **β-blocker** | **TD** |
| Medicines assessed | CTD vs losartan | HCTZ vs nifedipine; CTD vs amlodipine | HCTZ vs lisinopril; CTD vs lisinopril; CTD vs enalapril; HCTZ vs enalapril; HCTZ vs captopril | HCTZ vs propranolol; CTD vs propranolol | |

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CTD, chlorthalidone; HCTZ, hydrochlorothiazide; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life year; TD, thiazide-type diuretic.

## Table 2C

Summary of Cost Effectiveness of Antihypertensive Medicines From the Literature Published in 1990–2016: Comparison Within Medicine Class ($n$=13).

| Interventions | Controls | | | |
|---|---|---|---|---|
| ARB[a] | | | | |
| Olmesartan preferred | Candesartan | Irbesartan | Valsartan | Losartan |
| Comparison, *n* | 1 | 2 | 2 | 2 |
| ICER | NR | QALY: dominant | QALY: dominant | QALY: dominant |
| Candesartan preferred | Candesartan | Irbesartan | Valsartan | Losartan |
| Comparison, *n* | — | 1 | 1 | 2 |
| ICER | — | NR | NR | QALY: dominant |
| Telmisartan preferred | Candesartan | Irbesartan | Valsartan | Losartan |
| Comparison, *n* | 0 | 0 | 1 | 1 |
| ICER | — | — | QALY: $6,450–$34,678<br>LY: $10,275–$27,006 | QALY: $4,029–14,569<br>LY: $2,369–$9,457 |
| Irbesartan preferred | Candesartan | Irbesartan | Valsartan | Losartan |
| Comparison, *n* | 0 | — | 2 | 2 |
| ICER | — | — | QALY: dominant | QALY: dominant |
| Valsartan preferred | Candesartan | Irbesartan | Valsartan | Losartan |
| Comparison, *n* | 0 | 0 | — | 1 |
| ICER | — | — | — | QALY: $31,341–$33,567<br>LY: $22,448–$28,326 |
| Losartan preferred | Candesartan | Irbesartan | Valsartan | Losartan |
| Comparison, *n* | 1 | 0 | 0 | — |
| ICER | QALY: over threshold | — | — | — |
| CCB | | | | |
| Nifedipine preferred | Amlodipine | | | |
| Comparison, *n* | 1 | | | |
| ICER | NR | | | |
| β-blocker | | | | |
| Nebivolol preferred | Metoprolol | | | |
| Comparison, *n* | 1 | | | |
| ICER | NR | | | |
| Celiprolol preferred | Altenolol | | | |
| Comparison, *n* | 1 | | | |
| ICER | BP reduction: dominant | | | |

*Note:* ICER for QALY and LY were summarized.

[a]Among ARBs, no study used olmesartan and telmisartan as a control group.

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CTD, chlorthalidone; HCTZ, hydrochlorothiazide; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; TD, thiazide-type diuretic; QALY, quality-adjusted life year.