Aldosterone Synthase Inhibitors for the Treatment of Hypertension: Effectiveness and Value

Draft Evidence Report

AUGUST 12, 2026

Prepared for

ICER Staff and Consultants	University of Washington Modeling Team
Grace A. Lin, MD Medical Director for Health Technology Assessment Institute for Clinical and Economic Review **Dmitriy Nikitin, MSPH** Senior Research Lead Institute for Clinical and Economic Review **Marina Richardson, PhD, MSc** (Former) Director, Health Technology Assessment Methods and Health Economics Institute for Clinical and Economic Review **Marie Phillips, BA** Senior Health Economics Research Assistant Institute for Clinical and Economic Review **Sol Sanchez, BA** Research Assistant Institute for Clinical and Economic Review **David M. Rind, MD, MSc** Chief Medical Officer Institute for Clinical and Economic Review	**Kangho Suh, PharmD, PhD** Assistant Professor University of Pittsburgh, School of Pharmacy **Josh J. Carlson, PhD, MPH** Professor University of Washington, School of Pharmacy *The role of the University of Washington is limited to the development of the cost-effectiveness model, and the resulting ICER report does not necessarily represent the view of the University of Washington.*

ICER's value assessments are free from financial conflicts of interest from health care companies. As an organization, we value transparency and hold ourselves, and our collaborators, to high standards for conducting our work. Our full policy to manage potential conflicts of interest can be found here. You can find ICER's Code of Ethics here. Any conflicts reported by the authors of this report or expert reviewers can be found on page v.

DATE OF PUBLICATION: August 12, 2026

How to cite this document: Lin GA, Suh K, Nikitin D, Carlson JJ, Richardson M, Phillips M, Sanchez S, Rind DM. Aldosterone Synthase Inhibitors for the Treatment of Hypertension: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, August 12, 2026. https://icer.org/assessment/hypertension-2026/#overview.

Grace A. Lin served as the lead author for the report. Dmitriy Nikitin led the systematic review and authorship of the comparative effectiveness section of this report with assistance from Sol Sanchez. Kangho Suh and Josh J. Carlson developed the cost-effectiveness model and authored corresponding sections of the report with support from Marina Richardson. Marie Phillips conducted the analysis for the budget impact model. David M. Rind provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Madeline Booth, Hui-Hsuan Chan, Chloe Fandetti, and Anna Geiger and for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit ICER's website.

The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 20% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include AstraZeneca. A complete list of funders and more information on ICER's support is available on the funding page of the ICER website.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About Midwest CEPAC

The Midwest Comparative Effectiveness Public Advisory Council (CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care. The Midwest CEPAC Panel is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the initial draft evidence report:

Expert Reviewers

Andrew Bzowyckyj, PharmD, BCPS, CDCES
Senior Scientific Director, Learning Consultant
National Kidney Foundation

Jordana Cohen, MD, MSCE
Associate Professor of Medicine and Epidemiology
Perelman School of Medicine, University of Pennsylvania

Dhruv S. Kazi, MD, MSc, MS
Associate Director, Richard A. and Susan F. Smith Center for Outcomes Research
Director, Cardiac Critical Care Unit, Beth Isreal Deaconess Medical Center

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions or iterations of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from whom we requested input, or who have submitted public comments so far, please visit our website.

Conflict of Interest Disclosures for the Report

Table 1. ICER Authors and External Collaborators Conflict of Interest Disclosures

ICER Authors and External Collaborators	Conflict of Interest
Josh J. Carlson, PhD, MPH Professor University of Washington, School of Pharmacy	No conflicts to disclose.
Grace A. Lin, MD Medical Director for Health Technology Assessment Institute for Clinical and Economic Review	Grace Lin receives research grant funding via the University of California San Francisco from the National Institutes of Health, Mt. Zion Health Fund, GRAIL, Inc., and the California Health Benefits Research Program.
Dmitriy Nikitin, MSPH Senior Research Lead Institute for Clinical and Economic Review	No conflicts to disclose.
Marie Phillips, BA Health Economics Research Assistant Institute for Clinical and Economic Review	No conflicts to disclose.
Marina Richardson, PhD, MSc (Former) Director, Health Technology Assessment Methods and Health Economics Institute for Clinical and Economic Review	No conflicts to disclose.
David M. Rind, MD, MSc Chief Medical Officer Institute for Clinical and Economic Review	No conflicts to disclose.
Sol Sanchez, BA Research Assistant Institute for Clinical and Economic Review	No conflicts to disclose.
Kangho Suh, PharmD, PhD Assistant Professor University of Pittsburgh, School of Pharmacy	No conflicts to disclose.

Table 2. Expert Reviewers of the Report Conflict of Interest Disclosures

Expert Reviewer	Conflict of Interest
Andrew Bzowyckyj, PharmD, BCPS, CDCES Senior Scientific Director, Learning Consultant National Kidney Foundation	National Kidney Foundation receives 64% of their funding from health care companies including AstraZeneca.
Jordana Cohen, MD, MSCE Associate Professor of Medicine and Epidemiology Perelman School of Medicine, University of Pennsylvania	No conflicts to disclose.
Dhruv S. Kazi, MD, MSc, MS Associate Director, Richard A. and Susan F. Smith Center for Outcomes Research Director, Cardiac Critical Care Unit, Beth Israel Deaconess Medical Center	No conflicts to disclose.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

3-point MACE	3-point Major Adverse Cardiovascular Events
ACEi	Angiotensin-converting enzyme inhibitor
AE / AEs	Adverse event / Adverse events
ARB	Angiotensin II receptor blocker
ASI	Aldosterone synthase inhibitor
BAX	Baxdrostat
BPLTTC	Blood Pressure Lowering Treatment Trialists' Collaboration
CCB	Calcium channel blocker
CDR	Clinical Trial Diversity Rating
CHD	Coronary heart disease
CI	Confidence interval
CrI	Credible inerval
CKD	Chronic kidney disease
CV	Cardiovascular
DASH	Dietary Approaches to Stop Hypertension
eGFR	Estimated glomerular filtration rate
EPL	Eplerenone
ESKD	End-stage kidney disease
evLYs	Equal value life years
FDA	Food and Drug Administration
HDL	High-density lipoprotein
HIDI	Health Improvement Distribution Index
HR	Hazard ratio
ICER	Institute for Clinical and Economic Review
LDL	Low-density lipoprotein
LOR	Lorundrostat
MACE	Major adverse cardiovascular events
mEq/L	Milliequivalents per liter
mg	Milligrams
MI	Myocardial infarction
mL/min/1.73 m^2	Milliliters per minute per 1.73 square meters
mm Hg	Millimeters of mercury
mmol/L	Millimoles per liter
MRA	Mineralocorticoid receptor antagonist
N / n	Sample size / number of participants
NF	Non-fatal
NMA / NMAs	Network meta-analysis / Network meta-analyses
PDUFA	Prescription Drug User Fee Act
QALY	Quality-adjusted life year
RALES	Randomized Aldactone Evaluation Study
RCT / RCTs	Randomized controlled trial / Randomized controlled trials
RR	Relative risk / Risk ratio
SBP	Systolic blood pressure
SPIR	Spironolactone
SUCRA	Surface Under the Cumulative RAnking
UACR	Urine albumin-to-creatinine ratio
US	United States
WAC	Wholesale acquisition cost

Executive Summary

Hypertension, defined as a blood pressure consistently greater than or equal to 130/80 mm Hg (millimeters of mercury; blood pressure is also commonly written without units) is a very common chronic condition affecting nearly half of adults in the United States (US). Untreated, hypertension can result in end-organ damage such as strokes, heart attacks, or end-stage kidney disease (ESKD). Although decreasing blood pressure has been associated with improved outcomes, more than 70% of adults with hypertension continue to have a blood pressure above goal,[1] with African American, Hispanic, and Asian adults less likely to be at blood pressure goal compared to White adults in the US. Clinical inertia, pill burden, additive copays for multiple medications, variable tolerance for side effects, and a lack of awareness of the importance of treating hypertension can make treatment challenging. Hypertension is a contributing factor to over 600,000 deaths in the US each year,[2] with resultant medical costs estimated to be upwards of $219 billion annually.[3]

Treatment of hypertension typically involves lifestyle modifications (e.g., dietary modifications, increase in physical activity) and medications, which may be initiated at a systolic blood pressure ≥130 or 140 mm Hg, depending on cardiovascular risk. First-line antihypertensive medications include thiazide-type diuretics, long-acting dihydropyridine calcium channel blockers (CCB), and angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), which can all be used as monotherapy or in combination therapy.[4] For the almost seven million Americans estimated to have apparent treatment-resistant hypertension but not at blood pressure goal despite taking three or more medications, the addition of a mineralocorticoid receptor antagonist (MRA) such as spironolactone or eplerenone is recommended.[4] However, use of MRA medications is often limited by side effects, most prominently hyperkalemia and gynecomastia.

A new class of medications called aldosterone synthase inhibitors (ASI), which decreases production of aldosterone, has been developed to treat hypertension. This review is focused on two ASI drugs, baxdrostat (BAXFENDY™, AstraZeneca) and lorundrostat (Mineralys Therapeutics), that decrease production of aldosterone. We evaluated the net health benefits of baxdrostat and lorundrostat in three populations: (1) resistant hypertension not at goal; (2) blood pressure above goal while on two antihypertensive medications and did not tolerate a third first-line agent; and (3) blood pressure above goal despite use of two antihypertensive medications and who have not been treated with a third first-line agent.

We conducted network meta-analyses (NMA) in Populations 1 and 3; we did not find data for Population 2 and assumed baxdrostat and lorundrostat had the same effect in this population as in Population 1. For Population 1 (resistant hypertension), when compared to placebo, our NMA results demonstrated that the addition of baxdrostat, lorundrostat, spironolactone, eplerenone, or amiloride all produced a statistically significant decline in SBP (range -6.6 to -11 mm Hg). Neither baxdrostat nor lorundrostat resulted in statistically significant decreases in SBP over spironolactone,

eplerenone, or amiloride; however, 95% credible intervals were wide and included potentially clinically significant differences in both directions. Our NMA results for Population 3 demonstrated that baxdrostat, lorundrostat, and amlodipine produced statistically significant reductions in SBP versus no additional treatment (placebo) in patients already taking two antihypertensive medications (-8.3 to -10.1 mm Hg). However, neither baxdrostat nor lorundrostat showed a statistically significant difference in SBP reduction compared with amlodipine, with very small differences between the drugs. Overall harms for ASI drugs were similar, with hyperkalemia and hyponatremia among the more common side effects. Both ASI drugs appeared to be well-tolerated, though long-term data on harms are not available. Finally, there is not yet data on the direct impact of baxdrostat and lorundrostat on patient-important outcomes such as cardiovascular events, kidney disease, dementia, quality of life, or mortality; the other comparators in our review have demonstrated a positive impact on patient-important outcomes.

Despite effective blood pressure lowering, questions remain about the long-term effects of ASIs, as well as their impact on patient-important outcomes and their efficacy and safety in key subgroups (e.g., advanced chronic kidney disease). Our analyses of currently available data did not show differences in effect between ASIs; thus, for all three populations, current data are "insufficient" (**I**) to determine the net health benefits of baxdrostat and lorundrostat compared with each other. For patients with resistant hypertension not at goal and those on two antihypertensive medications who did not tolerate a third first-line treatment (Populations 1 and 2), our analyses found no statistically significant difference in blood-pressure lowering between all agents. However, ASIs such as baxdrostat and lorundrostat may be better tolerated than spironolactone and may result in greater blood pressure reductions than comparator drugs, though trials are only short-term. Thus, for these Populations, we conclude that the net health benefits of baxdrostat or lorundrostat are "Promising but Inconclusive" (**P/I**) compared with spironolactone, eplerenone, or amiloride. Finally, for the population of patients with hypertension not at goal on two antihypertensive medications who have not yet tried a third first-line agent (Population 3), our analyses demonstrated no statistically significant difference in blood pressure lowering between baxdrostat, lorundrostat, and amlodipine. In the absence of convincing outcomes data with the ASIs, we feel that, compared with amlodipine, the net health of baxdrostat or lorundrostat is "comparable or inferior" (**C-**). However, we acknowledge that there is uncertainty that is not fully captured by this rating and the rating could change with future evidence.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Populations 1 and 2*		
Baxdrostat	Lorundrostat	I
Baxdrostat or Lorundrostat	Spironolactone, Eplerenone, or Amiloride	P/I
Population 3†		
Baxdrostat	Lorundrostat	I
Baxdrostat or Lorundrostat	Amlodipine	C-

C-: "Comparable or Inferior", Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit; I: "Insufficient", Any situation in which the level of certainty in the evidence is low; P/I: "Promising but Inconclusive", Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit. Refer to the ICER Evidence Rating Matrix for more information.

*Population of patients with apparent treatment-resistant hypertension not at goal (Population 1) and the population of patients on two antihypertensive medications not at goal who cannot tolerate a third first-line medication (Population 2).

†Population of patients with hypertension not at goal on two antihypertensive medications who have not yet tried a third first-line agent (Population 3).

In cost-effectiveness analyses, treatment with baxdrostat and lorundrostat (at its placeholder price) generally provided small benefits in quality-adjusted life years (QALYs) and equal-value life-years (evLYs) compared to spironolactone, eplerenone, and amiloride, but at a much higher total cost. This led to incremental cost-effectiveness ratios that far exceeded commonly used thresholds (Table ES2). As baxdrostat and lorundrostat were comparable or inferior to amlodipine, we did not model this comparison.

Table ES2. Incremental Cost-Effectiveness Ratios

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained
Baxdrostat	Spironolactone	$833,000	$781,000
Baxdrostat	Eplerenone	$2,077,000	$1,954,000
Baxdrostat	Amiloride	$851,000	$800,000
Lorundrostat	Spironolactone	$1,419,000*	$1,327,000*
Lorundrostat	Eplerenone	More costly, less effective*	More costly, less effective*
Lorundrostat	Amiloride	$1,492,000*	$1,403,000*

evLY: equal-value life year, QALY: quality-adjusted life year

*Using a placeholder price for lorundrostat which is equivalent to baxdrostat price.

1. Background

Hypertension is a very common chronic condition, defined clinically by a blood pressure consistently greater than or equal to 130/80 mm Hg (millimeters of mercury; blood pressure is also commonly written without units). It affects nearly half of United States (US) adults, with higher rates in men and non-Hispanic African Americans.[5] Almost 20% of adults are not aware of their diagnosis, and nearly 34 million people who may need medications for treatment are not taking any.[6] The causes of hypertension are multifactorial, including genetics, environmental (e.g., air pollution), dietary influences (e.g., high sodium intake, alcohol), medical conditions (e.g., obesity, sleep disordered breathing, or kidney, thyroid or adrenal disease), and psychosocial stressors.[4] Although hypertension often does not cause symptoms, over time, the elevated pressure can damage arteries, resulting in a higher risk for heart attacks, strokes, chronic kidney disease, dementia, and heart failure.[7] It is a contributing factor to over 600,000 deaths in the US each year.[2] Medical costs resulting from hypertension in the US are estimated to be upwards of $219 billion annually.[3]

Treatment of hypertension involves both lifestyle changes and medications. Dietary modifications, such as the Dietary Approaches to Stop Hypertension (DASH) diet and reduction in salt intake, are recommended by clinical practice guidelines.[4] Reduction in salt intake has been associated with reductions in blood pressure of 2.1 to 11.5 mm Hg.[8] Other recommended non-pharmacologic interventions include weight loss (if overweight or obese), increased physical activity, reduction in alcohol use, and stress reduction.[4] Depending on cardiovascular risk level, clinical practice guidelines recommend initiating medication if systolic blood pressures are ≥130 or ≥140 mm Hg or diastolic blood pressures are ≥80 or ≥90 mm Hg.[4] First-line antihypertensive therapies include thiazide-type diuretics, long-acting dihydropyridine calcium channel blockers (CCB), and angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) and can be used as monotherapy or combination therapy. Decreasing blood pressure in persons with hypertension has been associated with improved outcomes; a meta-analysis of nearly 50 randomized, controlled trials demonstrated that a 5 mm Hg decrease in systolic blood pressure was associated with an around 10% decrease in major adverse cardiovascular events (MACE).[9] However, blood pressure is a surrogate marker and not all blood pressure drugs have the same effect on MACE, and their effects on mortality are also inconsistent.[10]

Despite effective treatments, more than 70% of adults with hypertension have not reached their goal blood pressure (i.e., blood pressure remains ≥130/80 mm Hg for most people),[1] with African American, Hispanic, and Asian adults less likely to be at blood pressure goal compared to White adults in the US.[5,11] There are many reasons for this: one survey of US adults showed that 31% were non-adherent to medications;[12] clinical inertia by physicians, difficulty accessing health care, lack of insurance, and having an underlying medical cause (secondary hypertension) are other

common causes of uncontrolled hypertension.[13,14] Almost seven million Americans are estimated to have apparent treatment-resistant hypertension, which is defined as a blood pressure above goal while a person is on three or more antihypertensive medications (ACEi/ARB + CCB + thiazide diuretic) at maximally tolerated doses or a blood pressure at goal on four or more antihypertensive medications.[4] For patients with resistant hypertension not at goal, the addition of a mineralocorticoid receptor antagonist (MRA) such as spironolactone or eplerenone is recommended.[4] However, use of spironolactone is often limited by side effects such as gynecomastia, and both spironolactone and eplerenone can result in high potassium levels. While there are alternative antihypertensive medications beyond MRAs, many of the other classes of agents (e.g., beta-blockers, alpha blockers, central sympatholytic drugs) tend to be less efficacious and less well-tolerated.[15]

A new class of medications called aldosterone synthase inhibitors (ASI) has been developed to treat hypertension. This review is focused on two ASI drugs, baxdrostat (AstraZeneca) and lorundrostat (Mineralys Therapeutics). Baxdrostat (BAXFENDY™) was approved by the US Food and Drug Administration (FDA) on May 18, 2026, for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adults who are not adequately controlled on other agents.[16] Lorundrostat is under consideration for approval by the US FDA for the treatment of hypertension, with a PDUFA date of December 22, 2026.[17] Unlike MRAs, which block the aldosterone receptor, ASI therapies decrease production of aldosterone. Aldosterone levels appear to be higher in patients with resistant hypertension,[18] and by decreasing production of aldosterone, ASI drugs may decrease blood pressure.

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Baxdrostat (BAXFENDY™)	Aldosterone synthase inhibitor	Oral	1 mg or 2 mg once daily*
Lorundrostat	Aldosterone synthase inhibitor	Oral	50 mg or 100 mg once daily†

mg: milligrams

*The recommended dosage of baxdrostat is 2 mg orally once daily, though 1 mg is recommended for patients at increased risk for hyperkalemia or hyponatremia.

†Lorundrostat is not yet FDA approved, dosages used in the clinical trials.

2. Patient and Other Stakeholder Perspectives

2.1. Patient Community Input

This draft report was developed with input from diverse stakeholders, including patients, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during calls with stakeholders and "Share Your Story" submissions to the ICER website. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of treatments for hypertension.

Although hypertension can result in end-organ damage such as strokes, heart attacks, or ESKD, many people living with hypertension do not have symptoms directly attributable to high blood pressure and thus have limited understanding of its consequences. We heard that some individuals with hypertension do not become aware of their condition until they have either severe hypertension (blood pressure higher than 180/120 mm Hg) or they have an event such as a heart attack, stroke, or develop kidney disease. Additionally, some individuals with hypertension report not being aware of how sodium intake may impact their health and the high sodium content of many foods; others report that they did not receive dietary counseling and/or referrals to resources such as a registered dietitian or nutritionist to help manage the disease. We also heard from people living with hypertension who felt that clinicians blamed them for difficulty controlling high blood pressure due to dietary indiscretions. We heard that there can be systemic barriers – e.g., food deserts, housing or food insecurity – that can prevent healthy lifestyle choices and cause chronic stress. Finally, we heard that peer education is important, as peer-to-peer interactions can reinforce physician messages on hypertension treatment.

After diagnosis, we heard that there can be treatment challenges that prevent people from reaching their blood pressure goal. For example, many people living with hypertension report needing to take multiple medications. While almost all antihypertensive medications have an available generic alternative and cost for individual drugs is rarely a barrier to adherence, pill burden, additive copays for multiple medications, variable tolerance for side effects such as frequent urination with diuretics or edema with calcium channel blockers, and a lack of awareness of the importance of treating hypertension – particularly in people without symptoms – can decrease adherence and persistence to treatment. We also heard that clinical inertia could result in suboptimal treatment of hypertension. For example, people living with hypertension told us that they had systolic blood pressure readings above 140 mm Hg at appointments, but their clinicians either did not address the reading and intensify therapy or told them that they did not need additional therapy. Additionally, patient groups mentioned that clinicians are often reluctant to start a fourth line medication like spironolactone because of potential side effects such as high

potassium and sexual side effects. People living with hypertension expressed hope that new medications would be more effective than older medications, allowing them to decrease the number of medications they need to take to control their blood pressure.

2.2. Health Equity Considerations

We heard that for people living with hypertension and chronic kidney disease, access to high-quality specialty care can be difficult due to geography, with some individuals needing to travel long distances to receive care at a tertiary care center. Additionally, we heard that although there may be differences in treatment effects by race or ethnicity, those differences are small and not likely to be clinically significant.

2.3. Clinical Input

Clinical experts emphasized that single pill combinations can help increase adherence to medications, but that some individuals with hypertension remain uncontrolled or have resistant hypertension even when they are taking medications regularly. For such individuals, mineralocorticoid receptor antagonists such as spironolactone are the preferred option; however, spironolactone may be difficult to take due to side effects, particularly for men. We also heard that there is clinical inertia when managing blood pressure and that it often takes three to six months to adjust or add a blood pressure medication, even in people with uncontrolled hypertension. Finally, we heard that chronic kidney disease can complicate treatment for hypertension, as each of the three first-line therapies have limitations in this population (e.g., potential decrease in efficacy with thiazide diuretics, or increased risk of side effects such as hyperkalemia with ACEi/ARBs, or difficult to treat edema from calcium-channel blockers).

2.4. Manufacturer Input

Manufacturers emphasized that the consequences of uncontrolled hypertension not only include cardiovascular and kidney events, but also an increased risk of dementia. They also suggested that quicker reductions in blood pressure to goal would have benefits, for example, in terms of workplace productivity. Manufacturers suggested that they viewed aldosterone synthase inhibitors as appropriate for either third or fourth-line therapy for patients with high blood pressure that are not at goal, regardless of whether patients had trialed a third first-line agent.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

We conducted a systematic literature review in April 2026; detailed methodology can be found in Supplement Section D1. A research protocol was published on Open Science Framework and is registered with PROSPERO (CRD420261371626).

Scope of Review

We evaluated the clinical effectiveness and safety of baxdrostat and lorundrostat as add-on therapies for the treatment of hypertension versus the following antihypertensive medications: spironolactone, eplerenone, amiloride, and amlodipine.

Our patient-important outcomes of interest included cardiovascular events, kidney outcomes, mortality, cognitive outcomes, retinopathy, and quality of life. We also evaluated the surrogate outcome of change in mean systolic blood pressure (SBP). Safety and tolerability outcomes of interest included serious adverse events, adverse events including gynecomastia, erectile dysfunction, electrolyte disturbances (e.g., sodium, potassium), and other treatment-related side effects.

The full scope of the review is described in Supplement Section D1.

Evidence Base

This review examined three distinct patient populations defined by their blood pressure control and treatment history:

- **Population 1:** Blood pressure above goal despite use of three or more antihypertensive medications at maximally tolerated doses (resistant hypertension not at goal).
    - We compared baxdrostat and lorundrostat with spironolactone, eplerenone, and amiloride.
- **Population 2:** Blood pressure above goal while on two antihypertensive medications and did not tolerate a third first-line agent recommended by clinical guidelines.
    - We compared baxdrostat and lorundrostat with spironolactone, eplerenone, and amiloride.
- **Population 3:** Blood pressure above goal despite use of two antihypertensive medications and who have not been treated with a third first-line agent recommended by clinical guidelines.
    - We compared baxdrostat and lorundrostat with amlodipine.

We conducted two network meta-analyses (NMA) in Populations 1 and 3. Based on data availability, we conducted the NMAs using the surrogate outcome of SBP. Because no trials of baxdrostat or lorundrostat met the Population 2 definition, we assumed the treatment effect was equivalent to that in Population 1 and used the Population 1 evidence for this population. We conducted all NMAs in a Bayesian framework using random-effects models. Supplement Section D2 describes the NMA methodology and sensitivity analyses. Supplement Table D1.6. presents the risk of bias assessment for studies within the network.

We identified thirteen relevant clinical trials for the Population 1 NMA, and eight trials were included in the Population 3 NMA. Two studies, BaxHTN and Launch-HTN, had available subgroup data and were included in both NMAs. A majority of the trials in our network were placebo-controlled and ranged from six to 26 weeks in treatment duration. Supplement Tables D2.2 and D3.1 summarize the baseline characteristics of participants and study design of these trials. Across study arms for both NMAs, participants had a mean or median age ranging from 53 to 67 years; 19.1% to 56.7% were female; baseline mean SBP was 134 to 167.9 mm Hg; mean eGFR was 44 to 98.4 mL/min/1.73 m^2. We did not identify any randomized controlled trials directly evaluating amlodipine as an add-on therapy in adults already on two antihypertensive medications. Instead, we estimated the isolated effect of amlodipine as a monotherapy on SBP using evidence from trials of triple-combination therapy by calculating the difference in SBP between triple-combination containing amlodipine and a dual-combination therapy without amlodipine. We used a similar approach to estimate the clinical effect of amiloride monotherapy in the PATHWAY-3 trial using the difference in SBP between the study arms of amiloride as a double-combination therapy and a thiazide monotherapy.

We reviewed additional studies that provided insight on patient-important outcomes (e.g., cardiovascular benefit) and safety profiles of the six therapies in our review. These studies and their findings are detailed in their respective sections below.

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of participants in the three pivotal trials of baxdrostat and lorundrostat (BaxHTN, Bax24, and Launch-HTN) using the ICER-developed Clinical trial Diversity Rating (CDR) Tool (Table 3.1).[19] All trials received a "fair" rating for race and ethnicity due to an underrepresentation of Black/African American or Asian participants. The lorundrostat trial received a "good" diversity rating for sex, whereas the baxdrostat trials received a "fair" diversity rating due to an underrepresentation of females. All trials received a "good" diversity rating for the representation of older adults (≥65 years). See Supplement D1 for full details of CDR methods and results.

Table 3.1. Diversity Ratings on Race and Ethnicity, Sex, and Age

Trial	Race and Ethnicity	Sex	Age (Older Adults)
Baxdrostat			
BaxHTN[20,21]	Fair	Fair	Good
Bax24[22]	Fair	Fair	Good
Lorundrostat			
Launch-HTN[23]	Fair	Good	Good

3.2. Results

Clinical Benefits

Systolic Blood Pressure

Population 1: Blood Pressure Above Goal Despite Use of Three or More Antihypertensive Medications at Maximally Tolerated Doses (Resistant Hypertension Not at Goal)

When compared to no additional treatment (placebo), our NMA results demonstrated that treatment with all five antihypertensive medications produced a statistically significant decline in SBP when studied as add-on therapy for resistant hypertension (Table 3.2). Although treatment with baxdrostat or lorundrostat did not result in statistically significant decreases in SBP over spironolactone, eplerenone, or amiloride, 95% credible intervals were wide and included potentially clinically significant differences in both directions.

There is limited evidence on the durability of treatment effects of either baxdrostat or lorundrostat. The longest study in our network of baxdrostat was 26 weeks. An open-label extension study of patients from an earlier baxdrostat Phase II trial, HALO, reported a mean change of -5.1 (standard deviation 11.51) in mean SBP from baseline to 52 weeks.[24] The longest available follow-up data for lorundrostat is 12 weeks, with an ongoing 52-week open-label extension study (See Supplement Table D4.1 for ongoing studies).

Table 3.2. Mean Differences in Systolic Blood Pressure (mm Hg) (Random Effects – Base Case)

Baxdrostat					
-0.9 (-5.7, 3.8)	Spironolactone				
-2 (-10.1, 6.2)	-1.1 (-8.9, 6.9)	Lorundrostat			
-2.2 (-9.5, 5.5)	-1.3 (-8.3, 6.3)	-0.2 (-9.8, 9.9)	Eplerenone		
-4.4 (-10.6, 1.8)	-3.5 (-8.4, 1.6)	-2.4 (-11.3, 6.4)	-2.2 (-10.7, 5.8)	Amiloride	
-11 (-14.6, -7.3)	**-10.1 (-13.1, -6.8)**	**-9 (-16.3, -1.7)**	**-8.9 (-15.5, -2.4)**	**-6.6 (-11.5, -1.5)**	Placebo

Note: Each box represents the estimated treatment difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. N=13 studies. Therapies ranked by Surface Under the Cumulative RAnking (SUCRA) curve values.

Population 2: Blood Pressure Above Goal While on Two Antihypertensive Medications and Did Not Tolerate a Third First-Line Agent Recommended by Clinical Guidelines

We did not identify any baxdrostat or lorundrostat studies that met the Population 2 definition. Instead, we used the Population 1 evidence for this population, assuming equivalent treatment effect based on two findings. First, subgroup analyses from baxdrostat and lorundrostat studies showed similar treatment effects among patients taking two versus three or more antihypertensive medications at baseline. Second, a meta-analysis of mineralocorticoid antagonists found no differential blood pressure lowering between resistant and non-resistant hypertension.[25]

Population 3: Blood Pressure Above Goal Despite Use of Two Antihypertensive Medications and Who Have Not Been Treated with a Third First-Line Agent Recommended by Clinical Guidelines

Our NMA results demonstrated that all three medications produced a statistically significant reduction in SBP versus no additional treatment (placebo) as add-on therapy in patients already taking two antihypertensive medications (Table 3.3). However, neither baxdrostat nor lorundrostat showed a statistically significant difference in SBP reduction compared with amlodipine, with very small differences between the drugs.

Table 3.3. Mean Differences in Systolic Blood Pressure (mm Hg) (Random Effects – Base Case)

Baxdrostat			
-1.5 (-9, 5.7)	**Lorundrostat**		
-1.8 (-8.6, 4.8)	-0.3 (-4.6, 4.1)	**Amlodipine**	
-10.1 (-16.6, -3.9)	**-8.6 (-12.4, -4.8)**	**-8.3 (-10.7, -6.2)**	**Placebo**

Note: Each box represents the estimated treatment difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. N=8 studies. Therapies ranked by Surface Under the Cumulative RAnking (SUCRA) curve values.

Patient Important Outcomes

Cardiovascular Effects

To date, there have been no published trials evaluating the impact of treatment with baxdrostat or lorundrostat on cardiovascular events. Baxdrostat is currently being evaluated in combination with dapagliflozin to determine its impact on the risk of incident heart failure and cardiovascular death (See Supplement Table D4.1 for ongoing studies).

We did not find any RCT sufficiently powered to assess patient-important cardiovascular outcomes (e.g., mortality, stroke, myocardial infarction [MI]) with spironolactone specifically in a hypertensive population.[26] Most outcomes data come from trials in a heart failure population (e.g., RALES, TOPCAT)[27,28] or are derived from subgroup/post-hoc analyses and observational data. Data from the largest observational study, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), demonstrated that after median follow-up of 3.7 years, spironolactone use in a resistant hypertension population

(N=8,776) was associated with lower risk of 3-point MACE [non-fatal stroke, non-fatal MI, and all-cause mortality] (HR 0.90; 95% Confidence Interval [CI]: 0.81 to 0.99) and all-cause mortality (HR 0.85; 95% CI: 0.75 to 0.96), compared to non-use. The point estimate for reduction in CV mortality was similar but was not statistically significant (HR 0.83; 95% CI: 0.68 to 1.01).[29] A real-world retrospective cohort study involving more than 80,000 patients with apparent treatment-resistant hypertension showed no reduction in stroke or acute MI associated with spironolactone compared with β blockers (metoprolol and atenolol) when used as fourth-line therapy.[30] We have some data on the impact of spironolactone treatment on the surrogate outcome of hypertensive retinopathy from the South Danish Hypertension and Diabetes Study. In participants with resistant hypertension and type 2 diabetes, retinopathy-related complications occurred in 39% of participants receiving spironolactone, compared to 45% receiving placebo.[31]

For eplerenone, there has not been an RCT sufficiently powered to assess cardiovascular outcomes (e.g., mortality, stroke, MI) specifically in a population with hypertension.[32] Most outcome data come from trials in heart failure or post-MI (EPHESUS, EMPHASIS-HF) [33,34] or are derived from subgroup/post-hoc analyses and observational data.

Two major trials have evaluated the cardiovascular benefits of amlodipine. In ALLHAT (N=42,418; mean follow-up 4.9 years), amlodipine 2.5 to 10 mg (n=9,048) showed no difference from chlorthalidone (n=15,255) in the primary outcome of fatal coronary heart disease or non-fatal MI (RR 0.98; 95% CI: 0.90 to 1.07) or all-cause mortality (RR: 0.96; 95% CI: 0.89 to 1.02).[35] In ASCOT-BPLA (N=19,257; median follow-up 5.5 years), treatment with amlodipine 5 to 10 mg/day plus perindopril as needed (amlodipine-based regimen; n=9,639) did not significantly reduce the primary endpoint of non-fatal MI or fatal coronary heart disease versus an atenolol-based regimen (HR 0.90; 95% CI: 0.79 to 1.02; p=0.11) but did significantly reduce stroke (HR 0.77; 95% CI: 0.66 to 0.89; p=0.0003), total cardiovascular events and procedures (HR 0.84; 95% CI: 0.78 to 0.90; p<0.0001), and all-cause mortality (HR 0.89; 95% CI: 0.81 to 0.99; p=0.025).[36]

Finally, we did not find any studies examining the effect of amiloride on cardiovascular outcomes in a population with hypertension.

Kidney Outcomes

There is no currently available evidence evaluating the impact of baxdrostat or lorundrostat on incident ESKD.

In the Phase II FigHTN trial, treatment with baxdrostat (0.5 to 4 mg/day) reduced urine albumin excretion by 55% compared with placebo. Hyperkalemia developed in 41% of participants on baxdrostat; however, most cases were mild to moderate.[37]

In the Phase II Explore-CKD trial, a low-dose of lorundrostat (25 mg/day) achieved a 25.6% placebo-adjusted reduction in geometric mean spot UACR (90% CI: -35.8 to -13.7; p=0.0015).[38] A subgroup analysis of LAUNCH-HTN participants with CKD reported that lorundrostat 50 mg/day reduced urine albumin by 52.2% compared to placebo (p<0.0001).[39]

We did not find any evidence on the impact of spironolactone on incident ESKD from the trials included in the NMA. An analysis of real-world data in a chronic kidney disease population found that treatment with spironolactone had no effect on the development of ESKD but resulted in increased risk of severe hyperkalemia and all-cause mortality.[40] However, spironolactone may have some positive effect on kidney function; in the South Danish Hypertension and Diabetes Study, spironolactone was associated with a lower rate of microalbuminuria, defined as 30 mg/g>UACR<300 mg/g, in patients with resistant hypertension and type 2 diabetes (28% of those receiving spironolactone vs. 42% in the placebo arm).[31]

We also did not find any evidence on the impact of eplerenone on incident ESKD. Data from RCTs on the surrogate endpoint of reduction in urinary albuminuria are mixed; one study in patients with hypertension but without diabetes found that eplerenone decreased urinary albuminuria by 27.6% compared with placebo and another found no difference in a resistant hypertension population.[41,42]

Amlodipine showed a comparable or superior effect to other treatments on reducing incident ESKD across several trials. A post-hoc analysis of the ALLHAT trial found that amlodipine had a similar effect to chlorthalidone in reducing the incidence of ESKD or a composite of ESKD and a 50% or greater decline in GFR.[43] In the VALUE trial, patients with hypertension at high cardiovascular risk received either valsartan or amlodipine, and both treatments had a similar effect on the incidence of ESKD.[44] The ACCOMPLISH trial showed that treatment with an ACE inhibitor (benazepril) plus amlodipine reduced the risk of kidney disease progression significantly more than treatment with an ACE inhibitor plus a diuretic (hydrochlorothiazide).[45]

The trials of amiloride included in our review did not include an assessment of the risk of ESKD.

Other Patient-Important Outcomes

We did not find any data on the impact on health-related quality of life, cognitive outcomes, or all-cause mortality for any of the therapies in our review.

Harms

Hyperkalemia

Hyperkalemia is a condition characterized by high levels of serum or plasma potassium, typically greater than 5-5.5 mEq/L.[46] First-line antihypertensive medications (i.e., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, potassium-sparing diuretics) and chronic kidney disease increase the risk of hyperkalemia, making it a common adverse effect in a hypertensive population.[46] Table 3.4 summarizes the rates of hyperkalemia reported in key trials or literature for the drugs of interest in our review that are associated with a risk of hyperkalemia. While rates associated with amiloride treatment were unavailable, amiloride has an FDA-box warning for hyperkalemia, either alone or in combination with hydrochlorothiazide.[47] In Pathway-3, 4.8% of participants who received amiloride monotherapy reported hyperkalemia.[48]

Table 3.4. Incidence of Hyperkalemia

Drug	Arm	n	Hyperkalemia, %
Baxdrostat*[49]	BAX 2 mg	441	10.2
	BAX 1 mg	333	6.6
	Placebo	442	2.5
Lorundrostat†[23,50]	LOR 50 mg	632	2.5
	Placebo	365	0.3
Spironolactone[51]	SPIR 15-50 mg	2748	17.5
	Placebo	2760	7.5
Eplerenone[51]	EPL 25-50 mg	5282	5
	Placebo	5275	2.6

BAX: baxdrostat, EPL: eplerenone, LOR: lorundrostat, mg: milligrams, n: number, SPIR: spironolactone

*Arms were pooled across BaxHTN, Bax24, and BrigHTN trials.

†Arms were pooled across Launch-HTN and Advance-HTN trials.

Across three key baxdrostat trials (BaxHTN, Bax24, BrigHTN), hyperkalemia was the most frequently reported adverse event (AE) and led to treatment discontinuation in 1.8% of participants in the 2 mg arm and 0.6% in the 1 mg arm, compared to none in the placebo group.[49] The FigHTN CKD trial reported hyperkalemia in 41% of participants with CKD receiving baxdrostat (pooled), compared to 5% in the placebo group.[37] The recommended dosage for patients at risk of hyperkalemia is 1 mg.[49]

Sex-Related Adverse Events

Gynecomastia, the enlargement of breast tissue in males, is a notable sex-related adverse effect of spironolactone.[52] In observational studies evaluating treatment for hypertension with spironolactone, gynecomastia rates ranged between 3.9 to 6%.[53] In the RALES trial in a heart failure population, 9% of male participants who received a mean dose of 26 mg developed gynecomastia.[54] There is a dose-dependent risk increase for gynecomastia, and onset can be as early as one to two months after starting treatment, but may take over a year to develop.[54]

Eplerenone has demonstrated lower rates of gynecomastia when compared to spironolactone, likely due to its selectivity for the aldosterone receptor.[53] In the EPHESUS trial testing eplerenone in patients with acute MI and heart failure, there were no significant differences between the eplerenone and placebo arms in terms of gynecomastia (0.5% vs. 0.6%) after a median follow-up time of 16 months.[53]

Evidence from head-to-head trials also suggest that gynecomastia occurs more frequently with spironolactone than eplerenone. A 2019 study in patients with resistant hypertension and CKD reported two cases of gynecomastia in the spironolactone arm, resulting in the participants switching to eplerenone treatment.[55] Another study found that, in patients with idiopathic hyperaldosteronism and hypertension, 11.8% of participants receiving spironolactone developed gynecomastia after 16 weeks of monotherapy, compared to none in the eplerenone group.[53]

Additional sex-related effects associated with MRAs include menstrual irregularities, reduced libido, and erectile dysfunction.[53] In a head-to-head trial of 208 adults with resistant hypertension, breast pain or tenderness, changes in libido, and menstrual irregularities were more frequently reported by those on spironolactone compared to eplerenone (5.2% and 1.9%, respectively).[56]

Hyponatremia

Hyponatremia is a condition characterized by low levels of plasma sodium (<135 mmol/L). Hyponatremia was seen across three key trials for baxdrostat, with the adverse event occurring in 3.2% of participants in the 2 mg arm, 2.1% in the 1 mg arm, and 0.9% in the placebo arm. Across the Launch-HTN and Advance-HTN trials, hyponatremia was the most frequently reported AE, occurring in 7.1% of participants treated with 50 mg lorundrostat versus 4.1% of those who received placebo.[23,50]

In Karns 2013, 6.1% of participants treated with eplerenone reported hyponatremia versus none in those who received placebo.[57]

Edema

Edema (i.e., swelling caused by fluid buildup) is an adverse effect commonly associated with amlodipine. Across placebo-controlled trials, amlodipine treatment (2.5 to 10 mg) resulted in 8.3% developing edema, compared to 2.4% in the placebo group.[58] There is a dose-dependent risk increase for edemas as rates increase from 1.8% to 10.3% with 2.5 to 10 mg doses, respectively.[58]

Other Harms

Additional adverse events that were reported in ≥2% of participants across three baxdrostat trials include hypotension, dizziness, and muscle spasms.[49]

Across the lorundrostat Launch-HTN and Advance-HTN trials, reduction in eGFR and symptomatic hypotension were reported in ≥2% of treated participants. Those that reported a reduction in eGFR required a dose modification (i.e., dose reduction, interruption, or discontinuation).[23,50]

Subgroup Analyses and Heterogeneity

We evaluated whether the treatment effect of baxdrostat or lorundrostat differed by subpopulations defined by sociodemographic (e.g., age, sex, and race/ethnicity) and clinical factors (baseline systolic blood pressure, body mass index, and kidney function [eGFR]).

In the BaxHTN and Bax24 studies, treatment effects between baxdrostat and placebo on SBP at week 12 were consistent across all prespecified subgroups (age, sex, race, ethnicity, geographic region, baseline SBP, eGFR, and BMI). See Supplement Table D6.1 for detailed point estimates across subgroups.

The Phase II FigHTN trial evaluated daily baxdrostat (low-dose: 0.5 mg up-titrated to 1 mg; high-dose: 2 mg up-titrated to 4 mg) in participants with CKD and uncontrolled hypertension (one-third were on an SGLT2 inhibitor).[37] The placebo-corrected mean change in SBP from baseline to week 26 was -8.1 mm Hg (95% CI: -13.4 to -2.8; p=0.003) in the pooled baxdrostat group. The low-dose group showed a reduction of -9.0 mm Hg (95% CI: -15.1 to -2.9; p=0.004), and the high-dose group showed a reduction of -7.2 mm Hg (95% CI: -13.2 to -1.2; p=0.02). Baxdrostat had no significant effect on eGFR; the change from baseline to week 26 was −2.3 mL/min/1.73 m² (95% CI: -5.1 to 0.5) in the pooled group versus placebo. The proportion of participants with a >30% eGFR decline between visits was comparable between baxdrostat (15%) and placebo (17%).

In the Launch-HTN study, treatment effects between lorundrostat and placebo at week six were consistent across the subgroups of age, sex, race, baseline SBP, BMI, waist-to-hip ratio, and eGFR (See Supplement Table D6.1).

The Phase II EXPLORE-CKD trial was a randomized, double-blind, placebo-controlled, crossover study in adults with uncontrolled hypertension and CKD (on stable SGLT2i and ACEi/ARB).[38] Participants received lorundrostat 25 mg/day or placebo in two four-week treatment periods separated by a 4-week washout. The mean placebo-corrected change in SBP from baseline was -7.5 mm Hg for lorundrostat (90% CI: -11.6 to -3.4; p=0.0024). Placebo-adjusted eGFR change was -4.6% (90% CI: -8.1 to -1.0; p=0.036). Three participants discontinued treatment due to four adverse events: hyperkalemia, acute kidney injury, retinal detachment, and CKD progression.

Uncertainty and Controversies

- Lack of data on patient-important outcomes: The pivotal trials for baxdrostat and lorundrostat measured short-term changes in systolic blood pressure, which is a surrogate endpoint. Although a reduction in blood pressure has been associated with an overall decrease in major adverse cardiac events (MACE) and progression of chronic kidney disease, not all drugs affect all components of MACE or decrease mortality.[10,60] Additional, longer-term data for baxdrostat and lorundrostat are necessary to determine their impact on patient-important outcomes.

- Lack of head-to-head trials: The pivotal trials for baxdrostat and lorundrostat are placebo-controlled, and thus comparison to each other, and to the other comparators in our review (spironolactone, eplerenone, amiloride, and amlodipine), is limited to indirect data from NMAs on blood pressure lowering. Thus, there is uncertainty in the relative efficacy and safety among the different medications. As there are several third- and fourth-line options for blood pressure lowering, direct comparison data would assist clinicians and patients in choosing the best options for treatment, particularly in terms of cardiovascular and kidney outcomes, and for side effects that may develop over longer periods of time (e.g., adrenal insufficiency). This is particularly true for Population 3, who would typically be prescribed a generic third first-line agent that has evidence proving it reduces cardiovascular and kidney events (e.g., amlodipine, ARB, or ACEi).

- Variability among studies in the NMAs: The trials included in the NMAs were varied in their method of blood pressure measurement, medication dosage, as well as duration of trials (some as short as six weeks), which may decrease the precision of our NMA estimates of blood pressure lowering. Additionally, we were unable to find placebo-controlled studies that examined the use of amlodipine as a third-line agent and instead estimated the effect of amlodipine based on studies of single-pill fixed combination therapies including amlodipine (triple therapy) compared with non-amlodipine dual combination therapy, which may not reflect real world conditions. Finally, due to data availability, some studies in our NMA were at higher risk of bias (e.g., open-label studies), which may affect the validity of our results.

- Lack of long-term data, particularly for important side effects: While 12 weeks may be enough to assess short-term blood pressure lowering for baxdrostat and lorundrostat, important questions regarding sustainment of blood pressure lowering, long-term tolerability, and safety remain. For example, baxdrostat was associated with an early decrease in eGFR, but whether or not this early change in eGFR adversely impacts long-term kidney function is not yet known. Additionally, the 12-week pivotal trials for baxdrostat and lorundrostat are not long enough to show whether clinically significant long-term adverse

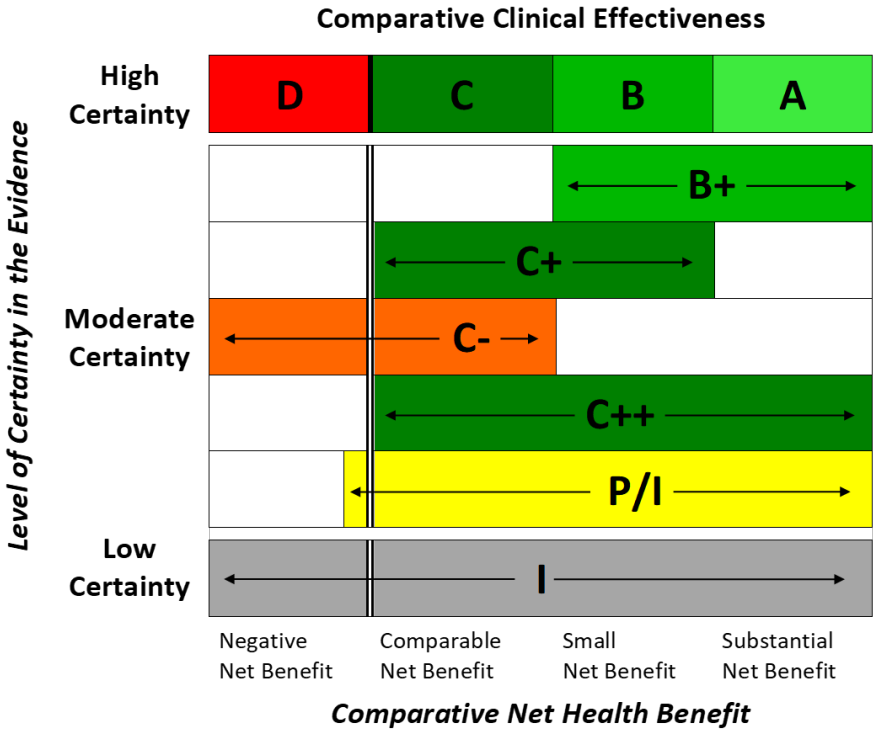
effects such as development of adrenal insufficiency are a concern with these drugs. We await data from extension studies of the pivotal trials to help answer such questions.

- Applicability of results to key subgroups: The pivotal trials for baxdrostat and lorundrostat excluded subgroups such as those with advanced chronic kidney disease. However, this subgroup is both one of high need (more likely to have difficulty controlling hypertension) and high risk for adverse events such as hyperkalemia. Ongoing studies may address whether ASIs are effective and safe in such subgroups.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Hypertension is a chronic disease that, if not controlled, can result in end-organ damage such as heart attack, stroke, dementia, and kidney disease. Although there are multiple classes of antihypertensive medications that have shown to be effective in lowering blood pressure, and in some cases reducing cardiovascular events, a large proportion of people with hypertension are undiagnosed or undertreated. For people with apparent treatment-resistant hypertension who are already taking three or more antihypertensive medications and are not at their goal blood pressure, fourth-line options may be limited by side effects such as hyperkalemia and gynecomastia. Thus, a new class of effective antihypertensive medications with a favorable side effect profile could help increase the number of patients with hypertension who reach their blood pressure goals and potentially see a decrease in cardiovascular or kidney events.

Our review focuses on two aldosterone synthase inhibitors: baxdrostat, which was recently approved by the FDA, and lorundrostat, which is under consideration by the FDA, for the treatment of resistant hypertension not at goal or hypertension that is not controlled on two or more agents. Pivotal trials demonstrated that both medications effectively lower blood pressure over 12 weeks with a tolerable safety profile. However, data on patient-important outcomes such as cardiovascular events and quality of life, are lacking.

For all populations, for the comparison of baxdrostat versus lorundrostat, we are relying on indirect evidence from short-term studies of blood pressure lowering, and qualitative comparison of safety and tolerability. Both agents appear to lower systolic blood pressure by a clinically meaningful amount. The NMA results are not able to differentiate whether one agent has superior blood pressure lowering over the other, but 95% credible intervals suggest that the possibility of clinically meaningful differences in blood pressure in either direction (i.e., baxdrostat superior to lorundrostat or vice versa). Both medications appear to have a similar safety profile; although more hyperkalemia was seen in the trials of baxdrostat, differences in the placebo rates of hyperkalemia across trials make this difference difficult to interpret. Neither medication has data on cardiovascular or kidney events. We conclude that for all populations, current data are "insufficient" (**I**) to determine the net health benefits of baxdrostat versus lorundrostat.

For the population of patients with apparent treatment-resistant hypertension not at goal (Population 1) and the population of patients on two antihypertensive medications not at goal who cannot tolerate a third first-line medication (Population 2), typical choices for the next agent to add to a patient's regimen would be spironolactone, eplerenone, or amiloride. Again, we lack head-to-head trials between baxdrostat and lorundrostat and these comparators, so our conclusions are drawn from indirect evidence including our NMAs. Although there appears to be no statistically significant difference in blood-pressure lowering between agents, there were small differences (2-4 mm Hg) between the ASI agents compared with eplerenone or amiloride that, if real, could over years result in clinically significant differences in outcomes. There is also the possibility that ASIs will demonstrate reduction in cardiac and kidney events. Finally, ASIs may be

more tolerable than MRAs, as they have lower rates of hyperkalemia than spironolactone (particularly lorundrostat) and no reported gynecomastia, although the trials may have been too short to detect other adverse events that may emerge over time (e.g., adrenal insufficiency). Compared with spironolactone, eplerenone, or amiloride, in patients with blood pressure not at goal who have either resistant hypertension or who are on two antihypertensive medications and cannot tolerate a third first-line medication, we conclude that the net health benefits of baxdrostat or lorundrostat are "Promising but Inconclusive" (**P/I**).

For the population of patients with hypertension not at goal on two antihypertensive medications who have not yet tried a third first-line agent (Population 3), our NMA demonstrated no statistically significant difference in blood pressure lowering between baxdrostat, lorundrostat, and amlodipine. Amlodipine does not carry a risk of electrolyte abnormalities, although edema can be a treatment-limiting side effect. Treatment with amlodipine has been shown to decrease major cardiovascular events, which has not yet been demonstrated for baxdrostat or lorundrostat. Based on available data, we have moderate certainty that amlodipine is not inferior to the ASIs, and if neither baxdrostat nor lorundrostat demonstrate the ability to reduce cardiovascular or kidney events, they would likely be inferior to amlodipine. However, it is also possible that baxdrostat or lorundrostat or both demonstrate larger cardiovascular or kidney benefits than amlodipine and/or that if the statistically non-significant ~2 mm Hg blood pressure lowering seen in the NMA is real, this could translate into clinical benefit over a lifetime. In the absence of convincing outcomes data with the new medications in patients not at goal on two antihypertensives who have not yet tried a third first-line agent, we feel that, compared with amlodipine, the net health of baxdrostat or lorundrostat is "comparable or inferior" (**C-**). However, we acknowledge that there is uncertainty that is not fully captured by this rating and the rating could change with future evidence.

Table 3.5. Evidence Ratings

Treatment	Comparator	Evidence Rating
Populations 1 and 2*		
Baxdrostat	Lorundrostat	I
Baxdrostat or Lorundrostat	Spironolactone, Eplerenone, or Amiloride	P/I
Population 3†		
Baxdrostat	Lorundrostat	I
Baxdrostat or Lorundrostat	Amlodipine	C-

C-: "Comparable or Inferior", Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit; I: "Insufficient", Any situation in which the level of certainty in the evidence is low; P/I: "Promising but Inconclusive", Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit.

*Population of patients with apparent treatment-resistant hypertension not at goal (Population 1) and the population of patients on two antihypertensive medications not at goal who cannot tolerate a third first-line medication (Population 2).

†Population of patients with hypertension not at goal on two antihypertensive medications who have not yet tried a third first-line agent (Population 3).

4. Long-Term Cost Effectiveness

4.1. Methods Overview

The primary aim of this analysis was to estimate the long-term cost-effectiveness of the aldosterone synthase inhibitors baxdrostat and lorundrostat for the treatment of hypertension. We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models.[61-65] Costs and outcomes were discounted at 3% per year. Model cycle length was three months. The analysis was conducted from a US health care sector perspective over a lifetime time horizon.

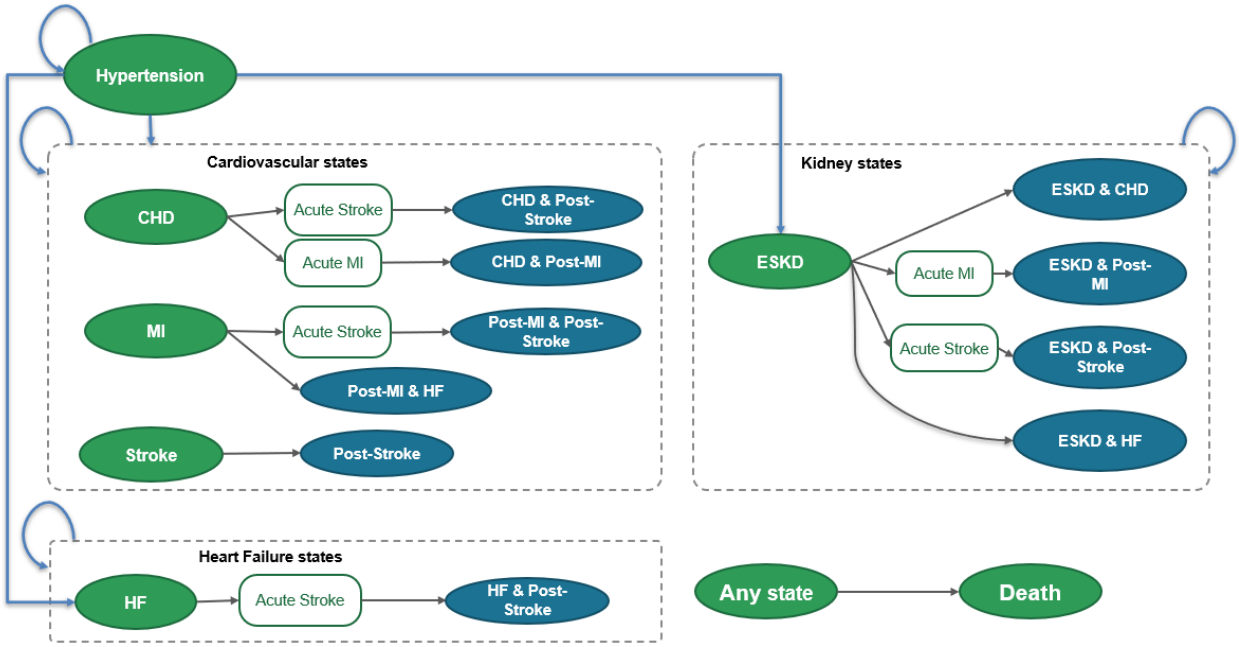
The clinical review evaluated three populations defined by blood pressure control and treatment history: Population 1 (blood pressure above goal despite three or more hypertensives at maximally tolerated doses representing resistant hypertension not at goal), Population 2 (blood pressure above goal on two antihypertensive agents, having not tolerated a third first-line agent), and Population 3 (blood pressure above goal on two antihypertensive agents, not yet treated with a third first-line agent). As in the clinical review, the Population 1 evidence was applied to Population 2 because no baxdrostat or lorundrostat trials met the Population 2 definition and the treatment effect was assumed to be equivalent (Section 3.2). Populations 1 and 2 were therefore reduced to a single modeled population. Population 3 was not modeled as the comparative effectiveness review rated baxdrostat and lorundrostat as "comparable or inferior" to amlodipine and, consistent with the Model Analysis Plan, cost-effectiveness in this population was to be evaluated only if the aldosterone synthase inhibitors were superior to amlodipine.

All patients entered the model in the hypertension alone health state and were treated with lorundrostat, baxdrostat, spironolactone, eplerenone, and amiloride. As shown in Figure 4.1, the model included seven primary health states 1) hypertension alone, 2) stroke, 3) myocardial infarction (MI), 4) other symptomatic coronary heart disease (CHD), 5) heart failure (HF), 6) end-stage kidney disease (ESKD), and 7) death. During each cycle, patients in the hypertension alone state remained there or transitioned to one of the cardiovascular or kidney event states, with transition probabilities derived from multivariate risk equations applied to each treatment's effect on systolic blood pressure (SBP). Patients also accumulated sequential events, moving through secondary health states such as post-MI and post-stroke. Heart failure arose from long-standing hypertension (primary HF) or followed a MI (secondary HF), and patients with CHD went on to experience an MI or stroke. The only exception was the post-stroke state, which acted as an absorbing state where patients could only transition to death. The model structure was adapted from prior economic evaluations of treatments for resistant hypertension.[62,63]

Patients remained in the model until they died. All patients transitioned to death from all causes from any of the alive health states. Patients died from age- and sex-specific all-cause mortality

drawn from US life tables, applied as the higher of background or disease-specific mortality in each cycle. Background mortality therefore predominated at older ages, once it exceeded health state-related mortality.

Figure 4.1. Model Structure



CHD: coronary heart disease, ESKD: end-stage kidney disease, HF: heart failure, MI: myocardial infarction

4.2. Key Model Assumptions and Inputs

Below is a list of key model choices:

- **Baseline transition probabilities**: probabilities of transitioning from the hypertension alone state to cardiovascular and kidney event states were derived from published multivariate risk equations.
- **Treatment effect mechanism:** each treatment's clinical benefit was modeled through its effect on systolic blood pressure, which was translated into cardiovascular and kidney event risk using event-specific hazard ratios from the Blood Pressure Lowering Treatment Trialists' Collaboration (stroke, ischemic heart disease, and heart failure per 5 mm Hg) and the corresponding risk reduction for ESKD, applied to the baseline transition probabilities.[9]
- **Sequential (i.e., combination) cardiovascular and kidney events:** following modeling precedent, only specific combinations were allowed, as shown in Figure 4.1. Prior models used this approach for parsimony and to capture the highest-probability combination health states.[62,63]

- **Elevated risks of cardiovascular events:** increased risks (hazard ratios of 1.44 post-MI and 3.4 in ESKD) were applied to the baseline transition probability for patients already in the post-MI or ESKD health state, to reflect their elevated risk of a subsequent cardiovascular events.[66,67] This increased risk remained the same regardless of the number of prior events.
- **Treatment discontinuation:** upon discontinuation, patients were modeled as returning to their baseline antihypertensive drugs. In clinical practice, patients would typically be treated with an additional (third or fourth) agent. While our model choice does not mirror clinical practice, it was a deliberate simplification to limit the influence of the choice of treatment sequence on the value assessment of each intervention. This simplification has been used in previous models.[62,68,69]

Our model includes several assumptions stated below (Table 4.1).

Table 4.1. Key Model Assumptions

Assumption	Rationale
Treatment effect persists while patients remain on therapy.	Consistent with prior models and clinical plausibility.[70,71] 10- and 20-year durations were tested in scenario analyses.
SBP reduction held constant after trial follow-up period.	Projecting further reductions beyond observed follow-up was not supported by current evidence.
BP returns to baseline immediately upon discontinuation.	Consistent with modeling precedent.[68,69] Pharmacologic effect ended with discontinuation.
RR reduction per mm Hg SBP lowering does not vary by baseline SBP.	Prior meta-regression found no evidence of effect modification by baseline SBP across any cardiovascular outcome.[9]
CV risk reduction per mm Hg SBP lowering is equivalent across drug classes.	In the absence of head-to-head RCT evidence, differences in cardiovascular outcomes between comparators were assumed to be driven solely by differences in achieved SBP reduction.

BP: blood pressure, CV: cardiovascular, mm Hg: millimeters of mercury, RCT: randomized controlled trial, RR: relative risk, SBP: systolic blood pressure

Published multivariate risk equations from prior models were used to establish the base probabilities of transitions from the hypertension alone state to each cardiovascular and kidney event states. Risk equations from the Framingham Heart Study were used for stroke, CHD, and HF, and PROCAM was used for MI. Prior models did not include a risk equation for ESKD so we estimated a three-month incidence probability of 0.14% from a previous study.[72] Additional details on the transition probabilities and inputs used for the risk equations can be found in the Supplement. Each treatment's effect was estimated and modeled through its SBP reduction from ICER's internal NMA (Table 4.2). These reductions were operationalized using the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) hazard ratios and relative risks per 5 or 10 mm Hg of SBP reduction, applied by health state, to the baseline transition probabilities generated by the risk equations.

Table 4.2. Treatment Effect Related Inputs

Parameter	Input	Source
SBP Reduction for Baxdrostat vs. Placebo	11.0 (95% CrI: 7.3, 14.6)	ICER's NMA
SBP Reduction for Lorundrostat vs. Placebo	9.0, (95% CrI: 1.7, 16.4)	ICER's NMA
SBP Reduction for Spironolactone vs. Placebo	10.1 (95% CrI: 6.7, 13.1)	ICER's NMA
SBP Reduction for Amiloride vs. Placebo	6.6 (95% CrI: 1.4, 11.6)	ICER's NMA
SBP Reduction for Eplerenone vs. Placebo	8.8 (95% CrI: 2.3, 15.5)	ICER's NMA
Hazard Ratio for Stroke, Per 5 mm Hg SBP Reduction	0.87 (95% CI: 0.84, 0.91)	BPLTTC 2021[9]
Hazard Ratio for Ischemic Heart Disease, Per 5 mm Hg SBP Reduction	0.92 (95% CI: 0.89, 0.95)	BPLTTC 2021[9]
Hazard Ratio for Heart Failure, Per 5 mm Hg SBP Reduction	0.87 (95% CI: 0.83, 0.92)	BPLTTC 2021[9]
Relative Risk for ESKD, Per 10 mm Hg SBP Reduction	0.95 (95% CI: 0.84, 1.07)	Ettehad et al. 2016[73]

BPLTTC: Blood Pressure Lowering Treatment Trialists' Collaboration, CI: confidence interval, CrI: credible interval, ESKD: end-stage kidney disease, mm Hg: millimeters of mercury, NMA: network meta-analysis, SBP: systolic blood pressure

All patients were subject to age- and sex-specific all-cause background mortality drawn from US life tables. For MI and stroke, we applied a one-time acute case fatality probability in the cycle in which the event occurs, reflecting the probability of dying from the event. Patients surviving the acute period were then subject to an ongoing per-cycle mortality risk for as long as they remained in the corresponding post-event state, rather than reverting to background mortality alone. Event-related mortality was applied through elevated, disease-specific mortality risk in the cycle following an acute cardiovascular event (MI and stroke) and through the ongoing mortality risk associated with the heart failure and ESKD states, consistent with prior hypertension models (Table 4.3).[62,63] In each cycle, the higher of the background or disease-specific mortality estimates was applied, so that background mortality predominated at older ages once it exceeds disease-specific mortality. For patients occupying more than one event state, the mortality risk of the higher (i.e., more severe) health state was applied consistently with a prior model.[63]

Table 4.3. Mortality Inputs

Parameter	Value	Source
Hypertension	Age and gender specific	US Life Table
Stroke (Acute, One Time / 3-Month)	Age-stratified (range from 4.1% age 60-69 up to 10.3% age 90+) / 7.00%	Fonarow et al. 2010[74] / Wang et al. 2023[75]
MI (Acute, One Time / 3-Month)	Age-stratified (range from 7.5% age 65-74 up to 22.0% age 85+) / Age-stratified (HR of 1.66 applied to general population)	Krumholz et al. 2014[76] / Wang et al. 2022[77]
Coronary Heart Disease (3-Month)	Age-stratified (range from 0.27% age less than 65 up to 1.51% age 75+)	Buckley et al. 2009[78]
Heart Failure (3-Month)	Age-stratified (range from 4.24% age 65-69 up to 17.51% age 90+)	Shah et al. 2017[79]
ESKD (3-Month)	Age-stratified (range from 3.30% age 45-64 up to 7.15% age 90+)	USRDS Annual Data Report (2025)[80]

ESKD: end-stage kidney disease, HR: hazard ratio, MI: myocardial infarction, US: United States

Note: For stroke and MI, the acute estimate is a one-time case fatality probability applied only in the cycle in which the event occurs. The post-event estimate is the ongoing risk applied in each subsequent cycle for as long as the patient survives in the corresponding post-event state. Because the two apply to different populations and time frames, they are not directly comparable, and the post-event estimate is expected to be lower than the acute estimate.

Note: Patients who experience multiple events will carry the higher mortality risk of the higher (i.e., more severe) health state.

Drug costs used are detailed in Table 4.4. For baxdrostat, we used the wholesale acquisition cost (WAC) price from RedBook ($900 for 30 tablets). Given that baxdrostat was recently launched, and no information is available to inform a discount from WAC, the WAC price was used as the net price. For lorundrostat, we used the baxdrostat WAC price as a placeholder price. For comparator drugs (spironolactone, eplerenone, and amiloride) we obtained net pricing estimates from Redbook based on the median cost (WAC) across all generic versions. No separate net price was estimated given the generic nature of the treatment.

Table 4.4. Drug Costs

Drug	WAC per Dose	Discount from WAC (if applicable)	Net Price per Dose	Net Price per Year
Spironolactone (25 mg)	$0.117	Not Applicable	$0.117	$43
Spironolactone (100 mg)	$0.4683	Not Applicable	$0.4683	$171
Eplerenone (50 mg)	$1.3997	Not Applicable	$1.3997	$511
Eplerenone (100 mg)	$2.793	Not Applicable	$2.793	$1,022
Amiloride (5 mg)	$0.5627	Not Applicable	$0.5627	$206
Amiloride (10 mg)	$1.1253	Not Applicable	$1.1253	$411

mg: milligrams, WAC: wholesale acquisition cost

Details on health state costs can be found in the Supplement.

Health state utilities were derived from publicly available literature (Table 4.5). Patients in the hypertension alone state were assigned an age-specific background utility for the US general population, consistent with prior models.[62,63,81-83] Disutilities for acute MI and acute stroke were informed by a United Kingdom general population study that valued these health states using the time trade-off method and was applied for one cycle (three months).[84] Utilities for the cardiovascular and kidney event states (stroke, MI, other CHD, heart failure, and ESKD) were drawn from Sullivan et al. (2006), a nationally representative US catalogue of preference-based health-state utilities for cardiovascular disease that has been used in prior ICER assessments involving cardiovascular disease health states.[85] The authors pooled the Medical Expenditure Panel Survey (MEPS) from 2000 to 2002 (38,678 adults) and estimated long-term utility scores for each condition using multivariate regression. For patients occupying more than one event state, a multiplicative approach was used to combine the relevant condition-specific utilities, consistent with standard practice in multi-state cost-effectiveness models.

Table 4.5. Health State Utilities

Parameter	Value	Source
Hypertension Alone	Age-specific	Jiang et al. 2021[86]
Acute MI, Disutility (3-Month)	-0.15	Matza et al. 2015[84]
Post-MI, Disutility	-0.041	Sullivan et al. 2006[85]
Acute Stroke, Disutility (3-Month)	-0.19	Matza et al. 2015[84]
Post-Stroke, Disutility	-0.052	Sullivan et al. 2006[85]
CHD, Disutility	-0.034	Sullivan et al. 2006[85]
HF, Disutility	-0.064	Sullivan et al. 2006[85]
ESKD, Disutility	-0.170	Gorodetskaya et al. 2005[87]
Combined Health States	Multiplicative approach	Calculated

CHD: coronary heart disease, ESKD: end-stage kidney disease, HF: heart failure, MI: myocardial infarction

4.3. Results

Base-Case Results

The total discounted costs, quality-adjusted life years (QALYs), equal value life years (evLYs), and life years (Lys) are detailed in Table 4.6 for all five treatment arms. Over a lifetime horizon, treatment with baxdrostat led to small evLY, QALY, and LY gains compared to the three comparators. Treatment with lorundrostat led to similar gains, except compared to eplerenone, where eplerenone had slightly better outcomes at a lower cost. Although lorundrostat produced slightly greater SBP reduction versus placebo than eplerenone did in the NMA (9.0 vs. 8.8 mm Hg), lorundrostat was modelled with higher discontinuation probability after three months or one cycle (10% based on LAUNCH-HTN) than eplerenone (7.7% from the literature-based persistence curve), which made it less effective and more costly than eplerenone in the base case. In a scenario analysis (Supplement Section E5), we assumed the same discontinuation probability for all five treatments.

Compared to the comparators, the total costs were higher for baxdrostat and lorundrostat, driven primarily by the higher drug costs. The clinical outcomes (MI, Stroke, CHD, HF, and ESKD events) were similar across all five treatments and are detailed in Supplement Section E3.

Table 4.6. Results for the Base-Case for Baxdrostat or Lorundrostat Compared to Spironolactone, Eplerenone, and Amiloride

Treatment	Intervention Acquisition Costs[†]	Non-Intervention Costs[‡]	Total Costs	Number of Strokes[§]	QALYs	evLYs	LYs
Baxdrostat	$27,600	$122,000	$149,600	150	9.55	9.55	11.87
Lorundrostat	$28,500*	$122,200	$150,700*	151	9.54	9.54	11.86
Spironolactone	$200	$122,600	$122,800	152	9.52	9.52	11.83
Eplerenone	$2,000	$122,200	$124,300	151	9.54	9.54	11.86
Amiloride	$830	$122,500	$123,400	152	9.52	9.52	11.84

evLYs: equal value life years, LY: life year, QALY: quality-adjusted life year

*Based on placeholder price.

[†]Included one-time costs of hyperkalemia monitoring ($11) for all five treatments.

[‡]Non-intervention costs include health state costs, dialysis and transplant charges, unrelated medical costs, and mortality costs associated with uncontrolled hypertension.

[§]Per 1,000 patients.

The incremental cost effectiveness ratios are detailed in Table 4.7.

Table 4.7. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Baxdrostat	Spironolactone	$833,000	$781,000	$712,000
Baxdrostat	Eplerenone	$2,077,000	$1,954,000	$1,774,000
Baxdrostat	Amiloride	$851,000	$800,000	$727,000
Lorundrostat	Spironolactone	$1,419,000*	$1,327,000*	$1,213,000*
Lorundrostat	Eplerenone	More costly, less effective*	More costly, less effective*	More costly, less effective*
Lorundrostat	Amiloride	$1,492,000*	$1,403,000*	$1,273,000*

evLYs: equal value life years, QALY: quality-adjusted life years

*Based on placeholder price.

Sensitivity Analyses

One-way sensitivity analyses were conducted on incremental evLYs gained and incremental total costs for all pairwise comparisons. Generally, the most influential parameters for all pairwise comparisons when assessing incremental evLYs gained and incremental total costs were the estimated SBP reduction for both the intervention and comparator, as well as the discontinuation assumption for baxdrostat and lorundrostat. The full one-way sensitivity analyses results are in the Supplement Section E4, in addition to the probabilistic sensitivity analyses.

Scenario Analyses

Scenario analyses focused on assumptions around treatment discontinuation. In one scenario, all interventions and comparators were subject to the same treatment discontinuation curve. In another, we assumed no discontinuation for any treatment. While the incremental cost-effectiveness ratios improved slightly in the modified societal and the same treatment discontinuation scenarios, they were still well-above commonly accepted threshold ranges. Additional scenario analyses detailed in the model analysis plan will be conducted in Section E5.

Threshold Analyses

Threshold analyses were conducted to calculate the annual cost of treatment needed to meet commonly accepted cost-effectiveness thresholds for QALY gained (Table 4.8) and evLY gained (Table 4.9).

Table 4.8. QALY-Based Threshold Analysis Results

Treatment	Comparator	Annual Net Price	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Baxdrostat	**Spironolactone**	$10,950	$960	$1,600	$2,200	$2,900
Baxdrostat	**Eplerenone**	$10,950	$1,100	$1,400	$1,600	$1,900
Baxdrostat	**Amiloride**	$10,950	$1,200	$1,800	$2,400	$3,000
Lorundrostat	**Spironolactone**	$10,950*	$600*	$980*	$1,400*	$1,700*
Lorundrostat	**Eplerenone**	$10,950*	$770*	$770*	$760*	$760*
Lorundrostat	**Amiloride**	$10,950*	$790*	$1,100*	$1,500*	$1,900*

QALY: quality-adjusted life year

*Based on placeholder price.

Table 4.9. evLY-Based Threshold Analysis Results

Treatment	Comparator	Annual Net Price	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Baxdrostat	**Spironolactone**	$10,950	$1,000	$1,700	$2,400	$3,000
Baxdrostat	**Eplerenone**	$10,950	$1,200	$1,400	$1,700	$1,900
Baxdrostat	**Amiloride**	$10,950	$1,200	$1,800	$2,500	$3,100
Lorundrostat	**Spironolactone**	$10,950*	$630*	$1,000*	$1,400*	$1,800*
Lorundrostat	**Eplerenone**	$10,950*	$770*	$770*	$760*	$760*
Lorundrostat	**Amiloride**	$10,950*	$810*	$1,200*	$1,600*	$1,900*

evLYs: equal value life years

*Based on placeholder price

Model Validation

Details on our model validation process can be found in Supplemental Section E6.

Prior Economic Models

Details on our comparison to prior economic models can be found in Supplemental Section E6.

Uncertainty and Controversies

There were several limitations and areas of uncertainty in our model:

- SBP reductions for each treatment were estimated from ICER's internal NMA rather than from head-to-head trials. Because these estimates relied on indirect comparisons rather than head-to-head evidence, several treatment effects, particularly lorundrostat, eplerenone, and amiloride, had wide credible intervals, representing uncertainty in the relative treatment effects that drove the cost-effectiveness results.

- The baxdrostat and lorundrostat trials measured SBP reductions rather than cardiovascular and kidney events. The model translated these reductions into changes in event risk using HRs and RR from the BPLTTC meta-analysis. The assumption that this SBP to event relationship applies to aldosterone synthase inhibitors is not confirmed.

- The baseline transition probabilities from the hypertension alone state to each cardiovascular and kidney event state were derived from published risk equations that were developed in cohorts that differed from our modeled uncontrolled and treatment-resistant hypertension population. However, the same risk equations and baseline transition probabilities were applied identically to all five treatments and largely cancelled the incremental comparisons that determine the cost-effectiveness results, which are instead driven by differences in SBP lowering.

- Trial-derived three-month discontinuation probabilities were applied in the first cycle for baxdrostat and lorundrostat, and an adverse-event–related discontinuation hazard ratio was applied to spironolactone. Beyond the first cycle, the same persistence function was applied to all treatments. While these assumptions may not perfectly capture real-world persistence, they were applied consistently across treatments.

- We were not able to include all hypertension related complications such as diabetes, obesity, atrial fibrillation, chronic kidney disease stages, and cognitive impairment, as data to include these in the model were either sparse or non-existent. However, because these events would be expected to accrue similarly across all treatment arms, their exclusion is unlikely to change the incremental results but may understate the absolute clinical and economic burden of disease.

4.4 Summary and Comment

Baxdrostat and lorundrostat produced clinically meaningful reductions in SBP in patients with uncontrolled and treatment-resistant hypertension, a population at elevated risk for cardiovascular and kidney events. The cost-effectiveness analyses indicated that baxdrostat and lorundrostat (at its placeholder price) generally provided small benefits in evLYs, QALYs, and LYs compared to the spironolactone, eplerenone, and amiloride, but at a higher total cost, largely from higher drug costs. The one exception was lorundrostat compared to eplerenone, which produced essentially equivalent QALYs and evLYs but at a higher cost, resulting in lorundrostat being more costly and less effective than eplerenone in the base case. At their current WAC-based price and placeholder price, the incremental cost-effectiveness ratios for baxdrostat and lorundrostat were well above commonly used cost-effectiveness thresholds.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the interventions in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There are particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies.	There are many antihypertensive medications available for treatment. However, it is estimated that among patients who are treated with medication, around 70% are not at their blood pressure goal.[88] Additionally, of patients with apparent treatment-resistant hypertension, around 60% are not at their blood pressure goal.[89] For patients who are not at their blood pressure goal, there may be an unmet need, depending on the severity of their hypertension and reason(s) for not achieving their blood pressure goal. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported for the modeled population below. The reference group is patients with uncontrolled hypertension not currently receiving the intervention or comparator drugs of interest for this review. evLY shortfalls: Absolute shortfall: 6.2 Proportional shortfall: 33% QALY shortfalls: Absolute shortfall: 5.5 Proportional shortfall: 31% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There are particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the health care system.	An estimated 120 million or 48.1% of US adults live with hypertension. The prevalence of hypertension was the highest in Non-Hispanic Black Americans (57.8%), and this group may benefit 1.2 times more than the overall population from access to effective blood pressure medications.
Apart from issues around disease severity/unmet need and race/ethnicity, there are other particular obligations to people with this condition.	Not applicable for this review.
The treatments are likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life.	The treatments may improve caregiver quality of life indirectly – if adequate treatment of blood pressure can prevent disability from cardiovascular disease, kidney disease, or cognitive decline, that could decrease caregiver burden.
If payment/cost were not an issue, the treatments are likely to improve access to treatment because of its method of delivery and/or treatment setting.	There are many oral antihypertensive medications currently available which are easily prescribed and obtained in the outpatient setting; new treatments are not likely to have an impact on access.

ICER calculated a Health Improvement Distribution Index (HIDI) and found that Black Americans have a higher proportion of hypertension, including resistant hypertension, than the general US population. The HIDI for Black Americans was 1.2, suggesting that any effective treatment may have a 20% greater impact in this population compared with the general US population. The HIDI for other racial and ethnic groups was either not substantially different from 1 or less than 1, meaning that an effective treatment would not have substantially different impacts in these populations as compared with the general US population.

6. Health Benefit Price Benchmark

ICER does not provide a Health Benefit Price Benchmark as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmark that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to calculate the total potential budgetary impact of baxdrostat and lorundrostat for the population of US adults with uncontrolled or resistant hypertension. Potential budget impact is defined as the total differential cost of using the new therapy rather than a relevant existing therapy for the treated population, calculated as health care costs (including drug costs) minus any offsets in these costs from averted health care events. We used an even split of spironolactone, eplerenone, and amiloride as the baseline comparator. All costs were undiscounted and estimated over a five-year time horizon. We used the net prices and the threshold prices (at $50,000, $100,000, $150,000, and $200,000 per evLY gained) for baxdrostat and lorundrostat when compared to each comparator to estimate the percentage of the eligible population that could be treated before reaching the ICER potential budget impact threshold of $821 million. Further details on ICER's approach to the budget impact analysis are available in Supplement Section F.

This budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment with baxdrostat and lorundrostat. This includes the resistant hypertension population consisting of those on three or more antihypertensive medications and not meeting blood pressure goals (Population 1), and the population on two antihypertensive medications and not meeting blood pressure goals who did not tolerate a third medication (Population 2). We did not estimate the budget impact for the population of those on two antihypertensive medications and not meeting blood pressure goals who have not tried a third first-line medication (Population 3) because this specific population was not modeled in the cost-effectiveness model.

To estimate the size of Population 1 (those taking three or more antihypertensive medications but still not achieving blood pressure goals), we used inputs for the overall prevalence of hypertension among US adults (48.1%),[5] the percentage of those with hypertension who are taking medication (51.2%),[90] and the percentage of those taking medication who are being treated with three or more antihypertensive medications but still have uncontrolled hypertension (15%).[91] Applying these sources to the overall adult population in the US averaged over the next five years (271,862,765) results in estimates of 10,042,828 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 2,008,565 patients per year.

To estimate the size of Population 2 (patients with hypertension on two medications and who attempted and discontinued a third antihypertensive medication population), we used inputs for the overall prevalence of hypertension among US adults (48.1%),[5] the percentage of those with hypertension who are taking medication (51.2%),[90] and the percentage of those taking medication

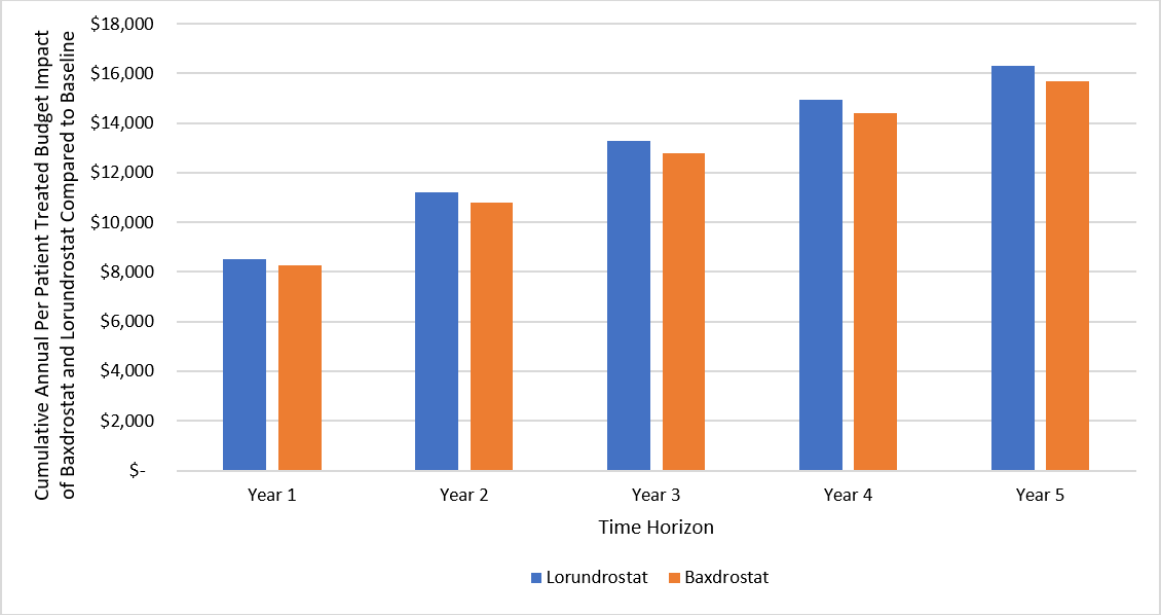
who are being treated with two antihypertensive medications and still have uncontrolled hypertension (17.9%).[91] We then assumed that 21% of these have attempted a third antihypertensive medication and discontinued. This is a placeholder estimate based on available claims data reporting discontinuation rate of antihypertensive medications.[92] As a result, we estimated that 2,516,732 patients have uncontrolled hypertension and have attempted and discontinued a third antihypertensive medication (Population 2). For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 503,346 patients per year. In total, between Population 1 and Population 2 we estimated a total of 12,559,560 eligible patients.

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated population budget impact for baxdrostat and lorundrostat, both compared to a baseline average of spironolactone, eplerenone, and amiloride. The cumulative per patient budget impact represents the incremental costs of each intervention compared to the baseline per patient across all patients treated within a time horizon (including those who initiated treatment in previous years), assuming baxdrostat and lorundrostat are used with 20% uptake each year over five years.

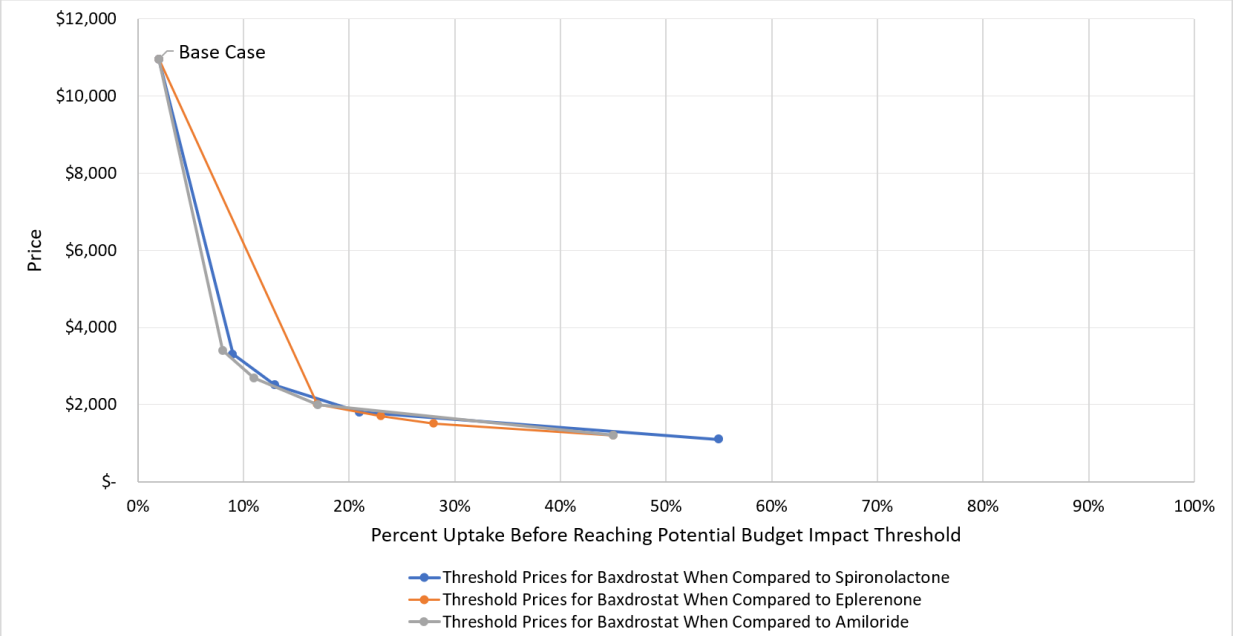
At baxdrostat's annual net price of $10,950, the cumulative annual budget impact per patient was approximately $8,300 in year one and $15,700 by year five. At lorundrostat's annual placeholder price of $10,950, the cumulative annual budget impact per patient was approximately $8,500 in year one and $16,300 by year five.

Figure 7.1. Cumulative Annual Per Patient Treated Budget Impact of Baxdrostat and Lorundrostat Compared to Baseline



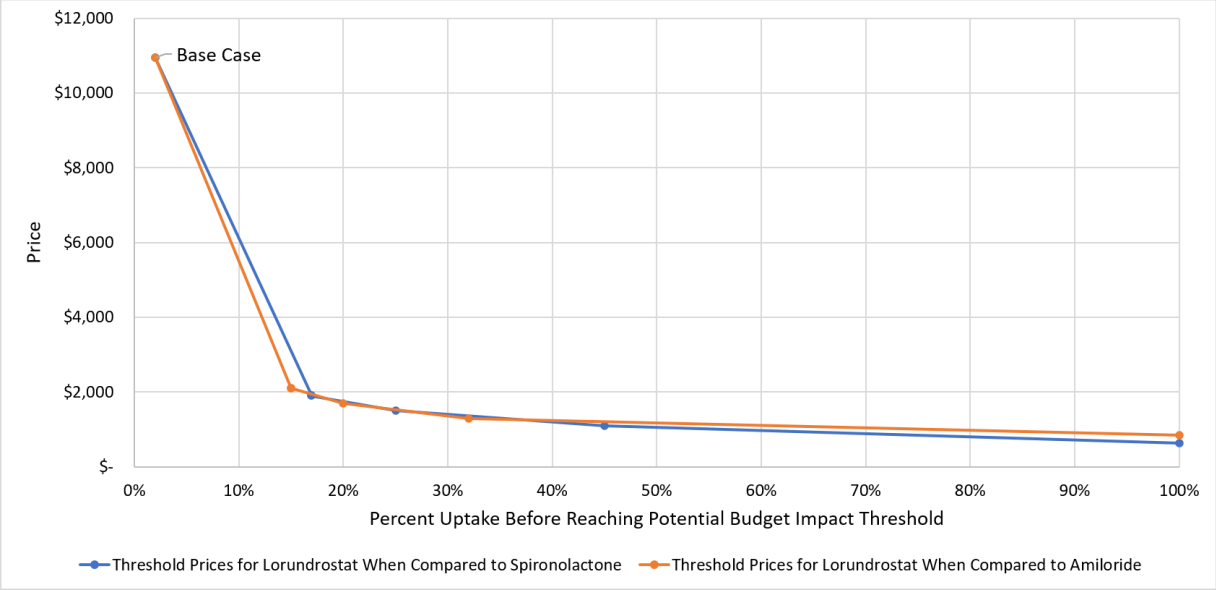
At the base case annual price of $10,950 for baxdrostat, approximately 2% of eligible patients (including both Population 1 and Population 2) could be treated before reaching the ICER potential budget impact threshold of $821 million. At the $50,000 per evLY threshold price when compared to spironolactone ($1,100), eplerenone ($1,200), and amiloride ($1,200), approximately 55%, 45%, and 45% of eligible patients could be treated respectively. At the $200,000 per evLY threshold price when compared to spironolactone ($3,300), eplerenone ($2,000), and amiloride ($3,400), approximately 9%, 17%, and 8% of eligible patients could be treated respectively. Figure 7.2 illustrates the percent uptake at each threshold price for baxdrostat.

Figure 7.2. Percent Uptake of Eligible Patients for Baxdrostat Before Reaching Potential Budget Impact Threshold



At the base case annual placeholder price of $10,950 for lorundrostat, approximately 2% of eligible patients (including both Population 1 and Population 2) could be treated before reaching the ICER potential budget impact threshold of $821 million. 100% of eligible patients could be treated at all threshold prices for lorundrostat when compared to eplerenone. 100% of the eligible population could also be treated at the $50,000 per evLY threshold price when compared to spironolactone ($630), and amiloride ($840). At the $200,000 per evLY threshold price when compared to spironolactone ($1,900) and amiloride ($2,100), approximately 17%, and 15% of eligible patients could be treated respectively. Figure 7.3 illustrates the percent uptake at each threshold price for lorundrostat.

Figure 7.3. Percent Uptake of Eligible Patients for Lorundrostat Before Reaching Potential Budget Impact Threshold



References

1. Earle WB, Watson NW, Juraschek SP, Cluett JL, Krawisz AK, Secemsky EA. Contemporary Prevalence and Treatment Patterns Among US Adults With Apparent Treatment-Resistant Hypertension. *Hypertension*. Jun 2026;83(6):e25659. doi:10.1161/HYPERTENSIONAHA.125.25659
2. National Center for Health Statistics. Multiple Cause of Death 2018-2023 on CDC WONDER Database. https://wonder.cdc.gov/mcd.html
3. Wang Y, Lee JS, Pollack LM, Kumar A, Honeycutt S, Luo F. Health Care Expenditures and Use Associated with Hypertension Among U.S. Adults. *Am J Prev Med*. Dec 2024;67(6):820-831. doi:10.1016/j.amepre.2024.07.005
4. Writing Committee M, Jones DW, Ferdinand KC, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM 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 Joint Committee on Clinical Practice Guidelines. *Hypertension*. Oct 2025;82(10):e212-e316. doi:10.1161/HYP.0000000000000249
5. Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guidance - NHANES 2017-2020. Accessed March 23, 2026, https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html
6. Johnson DY, Marinacci LX, Wadhera RK. Hypertension, Diabetes, and High Cholesterol Awareness Among US Adults. *JAMA Cardiol*. Aug 1 2025;10(8):859-860. doi:10.1001/jamacardio.2025.1536
7. Global Cardiovascular Risk C, Magnussen C, Ojeda FM, et al. Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality. *N Engl J Med*. Oct 5 2023;389(14):1273-1285. doi:10.1056/NEJMoa2206916
8. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. Jan 4 2001;344(1):3-10. doi:10.1056/NEJM200101043440101
9. Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. May 1 2021;397(10285):1625-1636. doi:10.1016/s0140-6736(21)00590-0
10. Wallach JD, Yoon S, Doernberg H, et al. Associations Between Surrogate Markers and Clinical Outcomes for Nononcologic Chronic Disease Treatments. *Jama*. May 21 2024;331(19):1646-1654. doi:10.1001/jama.2024.4175
11. Aggarwal R, Chiu N, Wadhera RK, et al. Racial/Ethnic Disparities in Hypertension Prevalence, Awareness, Treatment, and Control in the United States, 2013 to 2018. *Hypertension*. Dec 2021;78(6):1719-1726. doi:10.1161/HYPERTENSIONAHA.121.17570
12. Chang TE, Ritchey MD, Park S, et al. National Rates of Nonadherence to Antihypertensive Medications Among Insured Adults With Hypertension, 2015. *Hypertension*. Dec 2019;74(6):1324-1332. doi:10.1161/HYPERTENSIONAHA.119.13616
13. Ogedegbe G. Barriers to optimal hypertension control. *J Clin Hypertens (Greenwich)*. Aug 2008;10(8):644-6. doi:10.1111/j.1751-7176.2008.08329.x

14. Shea S, Misra D, Ehrlich MH, Field L, Francis CK. Predisposing factors for severe, uncontrolled hypertension in an inner-city minority population. *N Engl J Med*. Sep 10 1992;327(11):776-81. doi:10.1056/NEJM199209103271107
15. Lee CJ, Ihm SH, Shin DH, et al. Spironolactone vs Amiloride for Resistant Hypertension: A Randomized Clinical Trial. *Jama*. Jun 17 2025;333(23):2073-2082. doi:10.1001/jama.2025.5129
16. Baxdrostat New Drug Application accepted under FDA Priority Review in the US for patients with hard-to-control hypertension. December 2, 2025, https://www.astrazeneca.com/media-centre/press-releases/2025/baxdrostat-new-drug-application-accepted-under-fda-priority-review-in-the-us-for-patients-with-hard-to-control-hypertension.html#:~:text=If%20approved%2C%20baxdrostat%20could%20be%20the%20first,following%20use%20of%20a%20Priority%20Review%20voucher
17. Mineralys Therapeutics Announces FDA Acceptance of NDA for Lorundrostat for Treatment of Adults with Hypertension and Topline Explore-OSA Trial Results. March 9, 2026, https://www.sec.gov/Archives/edgar/data/1933414/000193341426000048/mlys202603068kex991.htm#:~:text=The%20FDA%20has%20assigned%20a%20Prescription%20Drug,especially%20for%20this%20difficult%20to%20control%20population
18. Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, et al. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. *Arch Intern Med*. Jun 9 2008;168(11):1159-64. doi:10.1001/archinte.168.11.1159
19. Agboola FW, AC. A Framework for Evaluating the Diversity of Clinical Trials. *Journal of Clinical Epidemiology*. 2024:111299.
20. Flack JM, Azizi M, Brown JM, et al. Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension. *N Engl J Med*. Oct 9 2025;393(14):1363-1374. doi:10.1056/NEJMoa2507109
21. Clinical Review of Baxfendy (baxdrostat) (2026).
22. Azizi M, Brown JM, Dwyer JP, et al. Effect of baxdrostat on ambulatory blood pressure in patients with resistant hypertension (Bax24): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet*. Mar 7 2026;407(10532):988-999. doi:10.1016/S0140-6736(25)02549-8
23. Saxena M, Laffin L, Borghi C, et al. Lorundrostat in Participants With Uncontrolled Hypertension and Treatment-Resistant Hypertension: The Launch-HTN Randomized Clinical Trial. *Jama*. Aug 5 2025;334(5):409-418. doi:10.1001/jama.2025.9413
24. AstraZeneca. Open-Label Extension Study of Patients Previously Enrolled in Study CIN-107-124. Updated December 16, 2024. https://clinicaltrials.gov/study/NCT05459688?tab=results#results-overview
25. Bazoukis G, Thomopoulos C, Tsioufis C. Effect of mineralocorticoid antagonists on blood pressure lowering: overview and meta-analysis of randomized controlled trials in hypertension. *J Hypertens*. May 2018;36(5):987-994. doi:10.1097/HJH.0000000000001671
26. Batterink J, Stabler SN, Tejani AM, Fowkes CT. Spironolactone for hypertension. *Cochrane Database Syst Rev*. Aug 4 2010;(8):CD008169. doi:10.1002/14651858.CD008169.pub2
27. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. Sep 2 1999;341(10):709-17. doi:10.1056/NEJM199909023411001
28. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. Apr 10 2014;370(15):1383-92. doi:10.1056/NEJMoa1313731
29. Prashar J, Hazewinkel D, Gregson J, et al. Efficacy of spironolactone in reducing the risk of cardiovascular events and long-term mortality in those with resistant hypertension: findings

from the Anglo-Scandinavian Cardiac Outcomes Trial. *European Heart Journal*. 2025;46(Supplement_1)doi:10.1093/eurheartj/ehaf784.3390
30. Desai R, Park H, Brown JD, Mohandas R, Pepine CJ, Smith SM. Comparative Safety and Effectiveness of Aldosterone Antagonists Versus Beta-Blockers as Fourth Agents in Patients With Apparent Resistant Hypertension. *Hypertension*. Oct 2022;79(10):2305-2315. doi:10.1161/HYPERTENSIONAHA.122.19280
31. Oxlund CS, Henriksen JE, Tarnow L, Schousboe K, Gram J, Jacobsen IA. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. *J Hypertens*. Oct 2013;31(10):2094-102. doi:10.1097/HJH.0b013e3283638b1a
32. Tam TS, Wu MH, Masson SC, et al. Eplerenone for hypertension. *Cochrane Database Syst Rev*. Feb 28 2017;2(2):CD008996. doi:10.1002/14651858.CD008996.pub2
33. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. Apr 3 2003;348(14):1309-21. doi:10.1056/NEJMoa030207
34. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. Jan 6 2011;364(1):11-21. doi:10.1056/NEJMoa1009492
35. Officers A, Coordinators for the ACRGTA, Lipid-Lowering Treatment to Prevent Heart Attack T. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Jama*. Dec 18 2002;288(23):2981-97. doi:10.1001/jama.288.23.2981
36. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. Sep 10-16 2005;366(9489):895-906. doi:10.1016/S0140-6736(05)67185-1
37. Dwyer JP, Maklad N, Vedin O, et al. Efficacy and Safety of Baxdrostat in Participants with CKD and Uncontrolled Hypertension: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Am Soc Nephrol*. Feb 1 2026;37(2):299-311. doi:10.1681/ASN.0000000849
38. Weir MR, Bhaduri S, Lee K, et al. Lorundrostat, a Novel Aldosterone Synthase Inhibitor (ASI), in Participants with Uncontrolled Hypertension, CKD, and Albuminuria: Results from Explore-CKD. *Journal of the American Society of Nephrology*. 2025;36(10S)doi:10.1681/ASN.202544j6mmcr
39. Vogt L, Heagerty P, Bhaduri S. Lorundrostat for Hypertension in CKD: Results From the LAUNCH-HTN Trial. 2026:
40. Chen TH, Ou SM, Lin KH, et al. Effect of spironolactone on cardiovascular and renal outcomes in patients with chronic kidney disease. *Clin Kidney J*. Sep 2025;18(9):sfaf247. doi:10.1093/ckj/sfaf247
41. Ando K, Ohtsu H, Uchida S, et al. Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. Dec 2014;2(12):944-53. doi:10.1016/S2213-8587(14)70194-9
42. Eguchi K, Kabutoya T, Hoshide S, Ishikawa S, Kario K. Add-On Use of Eplerenone Is Effective for Lowering Home and Ambulatory Blood Pressure in Drug-Resistant Hypertension. *J Clin Hypertens (Greenwich)*. Dec 2016;18(12):1250-1257. doi:10.1111/jch.12860

43. Adamczak M, Surma S, Wiecek A. Hyponatremia in patients with arterial hypertension: pathophysiology and management. *Arch Med Sci*. 2023;19(6):1630-1645. doi:10.5114/aoms/161578
44. Olsen E, Jamerson K, Schmieder RE, et al. Effects of valsartan vs amlodipine and achieved lower blood pressure on the incidence of end-stage kidney disease: The VALUE Trial. *Eur J Intern Med*. Mar 2025;133:55-63. doi:10.1016/j.ejim.2024.12.021
45. Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet*. Apr 3 2010;375(9721):1173-81. doi:10.1016/S0140-6736(09)62100-0
46. Chang AR, Sang Y, Leddy J, et al. Antihypertensive Medications and the Prevalence of Hyperkalemia in a Large Health System. *Hypertension*. Jun 2016;67(6):1181-8. doi:10.1161/HYPERTENSIONAHA.116.07363
47. Almajid AP, P; Cassagnol, M. Amiloride. *StatPearls [Internet]*. StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK542303/
48. Brown MJ, Williams B, Morant SV, et al. Effect of amiloride, or amiloride plus hydrochlorothiazide, versus hydrochlorothiazide on glucose tolerance and blood pressure (PATHWAY-3): a parallel-group, double-blind randomised phase 4 trial. *Lancet Diabetes Endocrinol*. Feb 2016;4(2):136-47. doi:10.1016/S2213-8587(15)00377-0
49. Highlights of Prescribing Information: BAXFENDY™ (2026).
50. Laffin LJ, Kopjar B, Melgaard C, et al. Lorundrostat Efficacy and Safety in Patients with Uncontrolled Hypertension. *N Engl J Med*. May 8 2025;392(18):1813-1823. doi:10.1056/NEJMoa2501440
51. Vukadinovic D, Lavall D, Vukadinovic AN, Pitt B, Wagenpfeil S, Bohm M. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: A meta-analysis. *Am Heart J*. Jun 2017;188:99-108. doi:10.1016/j.ahj.2017.03.011
52. Prisant LM, Chin E. Gynecomastia and hypertension. *J Clin Hypertens (Greenwich)*. Apr 2005;7(4):245-8. doi:10.1111/j.1524-6175.2005.04105.x
53. Danjuma MI, Mukherjee I, Makaronidis J, Osula S. Converging indications of aldosterone antagonists (spironolactone and eplerenone): a narrative review of safety profiles. *Curr Hypertens Rep*. Feb 2014;16(2):414. doi:10.1007/s11906-013-0414-8
54. Highlights of Prescribing Information: ALDACTONE® (2025).
55. Obertynska O. P4560The efficacy and safety of mineralocorticoid-receptor antagonists: spironolactone and eplerenone in resistant hypertension and chronic kidney disease stages 3. *European Heart Journal*. 2019;40(Supplement_1)doi:10.1093/eurheartj/ehz745.0951
56. Matova O, Mishchenko LA. The effect of spironolactone versus eplerenone on blood pressure targets in resistant hypertension patients. *European Heart Journal*. 2024;45(Supplement_1)doi:10.1093/eurheartj/ehae666.2592
57. Karns AD, Bral JM, Hartman D, Peppard T, Schumacher C. Study of aldosterone synthase inhibition as an add-on therapy in resistant hypertension. *J Clin Hypertens (Greenwich)*. Mar 2013;15(3):186-92. doi:10.1111/jch.12051
58. Highlights of Prescribing Information: NORVASC® (2011).
59. Calhoun DA, Lacourciere Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension*. Jul 2009;54(1):32-9. doi:10.1161/HYPERTENSIONAHA.109.131300

60. Lindholm LH CB, Samuelsson O. *Should beta blockers remain first choice in the treatment of primary hypertension: a meta-analysis.* Internet. Centre for Reviews and Dissemination (CRD); 2005. https://www.ncbi.nlm.nih.gov/books/NBK71704/
61. Dixon DL, Johnston K, Patterson J, Marra CA, Tsuyuki RT. Cost-Effectiveness of Pharmacist Prescribing for Managing Hypertension in the United States. *JAMA Netw Open*. Nov 1 2023;6(11):e2341408. doi:10.1001/jamanetworkopen.2023.41408
62. Geisler BP, Egan BM, Cohen JT, et al. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. *J Am Coll Cardiol*. Oct 2 2012;60(14):1271-7. doi:10.1016/j.jacc.2012.07.029
63. McFarlane PA, Madan M, Ryschon AM, et al. Cost-effectiveness analysis of radiofrequency renal denervation for uncontrolled hypertension in Canada. *J Med Econ*. Dec 2025;28(1):70-80. doi:10.1080/13696998.2024.2441072
64. Tajeu GS, Mennemeyer S, Menachemi N, Weech-Maldonado R, Kilgore M. Cost-effectiveness of Antihypertensive Medication: Exploring Race and Sex Differences Using Data From the REasons for Geographic and Racial Differences in Stroke Study. *Medical care*. Jun 2017;55(6):552-560. doi:10.1097/mlr.0000000000000719
65. Wang X, Chen H, E E, et al. Cost-effectiveness analysis of antihypertensive triple combination therapy among patients enrolled in a Medicare advantage plan. *Expert Rev Pharmacoecon Outcomes Res*. Aug 2021;21(4):829-836. doi:10.1080/14737167.2020.1800457
66. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J*. May 14 2015;36(19):1163-70. doi:10.1093/eurheartj/ehu505
67. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. Sep 23 2004;351(13):1296-305. doi:10.1056/NEJMoa041031
68. Bryan AS, Moran AE, Mobley CM, et al. Cost-effectiveness analysis of initial treatment with single-pill combination antihypertensive medications. *J Hum Hypertens*. Nov 2023;37(11):985-992. doi:10.1038/s41371-023-00811-3
69. Bryant KB, Rao AS, Cohen LP, et al. Effectiveness and Cost-Effectiveness of Team-Based Care for Hypertension: A Meta-Analysis and Simulation Study. *Hypertension*. Jun 2023;80(6):1199-1208. doi:10.1161/hypertensionaha.122.20292
70. Delea TE, Sofrygin O, Palmer JL, et al. Cost-effectiveness of aliskiren in type 2 diabetes, hypertension, and albuminuria. *J Am Soc Nephrol*. Oct 2009;20(10):2205-13. doi:10.1681/asn.2008111144
71. Richman IB, Fairley M, Jørgensen ME, Schuler A, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of Intensive Blood Pressure Management. *JAMA Cardiol*. Nov 1 2016;1(8):872-879. doi:10.1001/jamacardio.2016.3517
72. Kim H, Park YM, Ko SH, et al. Blood pressure levels and risk of end-stage renal disease in patients with type 2 diabetes who underwent percutaneous coronary intervention: a nationwide population-based study. *Sci Rep*. Mar 6 2025;15(1):7832. doi:10.1038/s41598-025-91835-x
73. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. Mar 5 2016;387(10022):957-967. doi:10.1016/s0140-6736(15)01225-8
74. Fonarow GC, Reeves MJ, Zhao X, et al. Age-related differences in characteristics, performance measures, treatment trends, and outcomes in patients with ischemic stroke. *Circulation*. Feb 23 2010;121(7):879-91. doi:10.1161/circulationaha.109.892497

75. Wang Y, Leifheit EC, Goldstein LB, Lichtman JH. Association of short-term hospital-level outcome metrics with 1-year mortality and recurrence for US Medicare beneficiaries with ischemic stroke. *PLoS One*. 2023;18(8):e0289790. doi:10.1371/journal.pone.0289790
76. Krumholz HM, Normand SL, Wang Y. Trends in hospitalizations and outcomes for acute cardiovascular disease and stroke, 1999-2011. *Circulation*. Sep 16 2014;130(12):966-75. doi:10.1161/circulationaha.113.007787
77. Wang Y, Leifheit EC, Krumholz HM. Trends in 10-Year Outcomes Among Medicare Beneficiaries Who Survived an Acute Myocardial Infarction. *JAMA Cardiol*. Jun 1 2022;7(6):613-622. doi:10.1001/jamacardio.2022.0662
78. Buckley BS, Simpson CR, McLernon DJ, Murphy AW, Hannaford PC. Five year prognosis in patients with angina identified in primary care: incident cohort study. *Bmj*. Aug 6 2009;339:b3058. doi:10.1136/bmj.b3058
79. Shah KS, Xu H, Matsouaka RA, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol*. Nov 14 2017;70(20):2476-2486. doi:10.1016/j.jacc.2017.08.074
80. United States Renal Data System. *2025 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. , 2025. https://usrds-adr.niddk.nih.gov/2025
81. Penko JM, Bellows BK, Hennessy S, et al. Cost-Effectiveness of Hypertension Treatment According to 2017 American College of Cardiology and American Heart Association Guidelines. *Circ Cardiovasc Qual Outcomes*. Aug 2025;18(8):e011872. doi:10.1161/circoutcomes.124.011872
82. Liao CT, Toh HS, Sun L, et al. Cost-effectiveness of Intensive vs Standard Blood Pressure Control Among Older Patients With Hypertension. *JAMA Netw Open*. Feb 1 2023;6(2):e230708. doi:10.1001/jamanetworkopen.2023.0708
83. Constanti M, Floyd CN, Glover M, Boffa R, Wierzbicki AS, McManus RJ. Cost-Effectiveness of Initiating Pharmacological Treatment in Stage One Hypertension Based on 10-Year Cardiovascular Disease Risk: A Markov Modeling Study. *Hypertension*. Feb 2021;77(2):682-691. doi:10.1161/hypertensionaha.120.14913
84. Matza LS, Stewart KD, Gandra SR, et al. Acute and chronic impact of cardiovascular events on health state utilities. *BMC Health Serv Res*. Apr 22 2015;15:173. doi:10.1186/s12913-015-0772-9
85. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making*. Jul-Aug 2006;26(4):410-20. doi:10.1177/0272989x06290495
86. Jiang R, Janssen MFB, Pickard AS. US population norms for the EQ-5D-5L and comparison of norms from face-to-face and online samples. *Qual Life Res*. Mar 2021;30(3):803-816. doi:10.1007/s11136-020-02650-y
87. Gorodetskaya I, Zenios S, McCulloch CE, et al. Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney Int*. Dec 2005;68(6):2801-8. doi:10.1111/j.1523-1755.2005.00752.x
88. (CDC) CfDCaP. High Blood Pressure Facts. Updated June 2, 2026. https://www.cdc.gov/high-blood-pressure/data-research/facts-stats/index.html
89. Ammann EM, O'Brien ES, Milentijevic D, et al. Characteristics, management, and blood pressure control in patients with apparent resistant hypertension in the US. *Heliyon*. Feb 2023;9(2):e13258. doi:10.1016/j.heliyon.2023.e13258
90. Centers for Disease Control and Prevention (CDC). Hypertension Prevalence, Awareness, Treatment, and Control Among Adults Age 18 and Older: United States, August 2021–August 2023. https://www.cdc.gov/nchs/products/databriefs/db511.htm?

91. Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P. Prevalence of Apparent Treatment-Resistant Hypertension in the United States. *Hypertension*. 2019;73(2):424-431. doi:doi:10.1161/HYPERTENSIONAHA.118.12191
92. Tajeu GS, Kent ST, Kronish IM, et al. Trends in Antihypertensive Medication Discontinuation and Low Adherence Among Medicare Beneficiaries Initiating Treatment From 2007 to 2012. *Hypertension*. Sep 2016;68(3):565-75. doi:10.1161/hypertensionaha.116.07720
93. Association AH. Understanding Blood Pressure Readings. Accessed June 15, 2026. https://www.heart.org/en/health-topics/high-blood-pressure/understanding-blood-pressure-readings
94. (CDC) CfDCaP. Measuring Your Blood Pressure. Updated May 12, 2026. https://www.cdc.gov/high-blood-pressure/measure/index.html
95. Guirguis-Blake JM, Evans CV, Webber EM, Coppola EL, Perdue LA, Weyrich MS. Screening for Hypertension in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama*. Apr 27 2021;325(16):1657-1669. doi:10.1001/jama.2020.21669
96. Cepeda M, Pham P, Shimbo D. Status of ambulatory blood pressure monitoring and home blood pressure monitoring for the diagnosis and management of hypertension in the US: an up-to-date review. *Hypertens Res*. Mar 2023;46(3):620-629. doi:10.1038/s41440-022-01137-2
97. Inker LA, Titan S. Measurement and Estimation of GFR for Use in Clinical Practice: Core Curriculum 2021. *Am J Kidney Dis*. Nov 2021;78(5):736-749. doi:10.1053/j.ajkd.2021.04.016
98. Foundation NK. Chronic Kidney Disease (CKD). Updated September 11, 2023. Accessed June 29, 2026, https://www.kidney.org/kidney-topics/chronic-kidney-disease-ckd
99. (CDC) CfDCaP. Chronic Kidney Disease Basics. Updated May 15, 2024. Accessed June 29, 2026, https://www.cdc.gov/kidney-disease/about/index.html
100. Ottersen T, Førde R, Kakad M, et al. A new proposal for priority setting in Norway: Open and fair. *Health Policy*. Mar 2016;120(3):246-51. doi:10.1016/j.healthpol.2016.01.012
101. van de Wetering EJ, Stolk EA, van Exel NJ, Brouwer WB. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *Eur J Health Econ*. Feb 2013;14(1):107-15. doi:10.1007/s10198-011-0346-7
102. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *Pharmacoeconomics*. 2004;22(17):1097-107. doi:10.2165/00019053-200422170-00001
103. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med*. Mar 1 1997;126(5):376-80.
104. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current
105. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
106. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
107. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. Updated January 31, 2020. https://icer.org/evidence-rating-matrix/
108. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care*. Jun 2010;48(6 Suppl):S145-52. doi:10.1097/MLR.0b013e3181d9913b

109. Kumbhani DJ. Efficacy and Safety of Baxdrostat in Patients With Uncontrolled Hypertension - HALO. July 16, 2026. https://www.acc.org/latest-in-cardiology/clinical-trials/2023/03/01/23/34/halo
110. CinCor Pharma I. A Study of CIN-107 in Patients With Uncontrolled Hypertension (HALO). Updated August 1, 2023. https://clinicaltrials.gov/study/NCT05137002
111. Freeman MW, Halvorsen YD, Marshall W, et al. Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension. *N Engl J Med*. Feb 2 2023;388(5):395-405. doi:10.1056/NEJMoa2213169
112. Laffin LJ, Rodman D, Luther JM, et al. Aldosterone Synthase Inhibition With Lorundrostat for Uncontrolled Hypertension: The Target-HTN Randomized Clinical Trial. *Jama*. Sep 26 2023;330(12):1140-1150. doi:10.1001/jama.2023.16029
113. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. Nov 21 2015;386(10008):2059-2068. doi:10.1016/S0140-6736(15)00257-3
114. Václavík J, Sedlak R, Jarkovsky J, Kocianova E, Taborsky M. Effect of spironolactone in resistant arterial hypertension: a randomized, double-blind, placebo-controlled trial (ASPIRANT-EXT). *Medicine (Baltimore)*. Dec 2014;93(27):e162. doi:10.1097/MD.0000000000000162
115. Ni X, Zhang J, Zhang P, et al. Effects of spironolactone on dialysis patients with refractory hypertension: a randomized controlled study. *J Clin Hypertens (Greenwich)*. Sep 2014;16(9):658-63. doi:10.1111/jch.12374
116. Oparil S, Melino M, Lee J, Fernandez V, Heyrman R. Triple therapy with olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide in adult patients with hypertension: The TRINITY multicenter, randomized, double-blind, 12-week, parallel-group study. *Clin Ther*. Jul 2010;32(7):1252-69. doi:10.1016/j.clinthera.2010.07.008
117. Rakugi H, Tsuchihashi T, Shimada K, et al. Efficacy and safety of fixed-dose losartan/hydrochlorothiazide/amlodipine combination versus losartan/hydrochlorothiazide combination in Japanese patients with essential hypertension. *Clin Exp Hypertens*. 2015;37(3):260-6. doi:10.3109/10641963.2014.954712
118. Higaki J, Komuro I, Shiki K, et al. The efficacy and long-term safety of a triple combination of 80 mg telmisartan, 5 mg amlodipine and 12.5 mg hydrochlorothiazide in Japanese patients with essential hypertension: a randomized, double-blind study with open-label extension. *Hypertens Res*. Jan 2017;40(1):51-60. doi:10.1038/hr.2016.100
119. Mineralys Therapeutics Announces Late-Breaking Data from Advance-HTN Pivotal Trial of Lorundrostat in Uncontrolled and Resistant Hypertension Presented at the American College of Cardiology's Annual Scientific Session & Expo (ACC.25). March 29, 2025, 2025. https://ir.mineralystx.com/news-events/press-releases/detail/66/mineralys-therapeutics-announces-late-breaking-data-from
120. Tian Z, Vollmer Barbosa C, Lang H, Bauersachs J, Melk A, Schmidt BMW. Efficacy of pharmacological and interventional treatment for resistant hypertension: a network meta-analysis. *Cardiovasc Res*. Feb 27 2024;120(1):108-119. doi:10.1093/cvr/cvad165
121. Dewi IP, Anggitama AM, Jati EB, Dewi KP. Comparative efficacy and safety of aldosterone synthase inhibitors in hypertension: a Bayesian network meta-analysis of randomised controlled trials. *Open Heart*. Oct 15 2025;12(2)doi:10.1136/openhrt-2025-003535
122. Elbahloul MA, Ali AHG, Al-Shammari AS, et al. Aldosterone synthase inhibitors for resistant or uncontrolled hypertension: a network meta-analysis of randomized clinical trials. *J Hypertens*. Apr 1 2026;44(4):542-552. doi:10.1097/HJH.0000000000004264

123. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama*. Sep 13 2016;316(10):1093-103. doi:10.1001/jama.2016.12195
124. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2019;22(8):931-941. doi:10.1016/j.jval.2019.02.009
125. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. Mar 1991;22(3):312-8. doi:10.1161/01.str.22.3.312
126. Voss R, Cullen P, Schulte H, Assmann G. Prediction of risk of coronary events in middle-aged men in the Prospective Cardiovascular Münster Study (PROCAM) using neural networks. *Int J Epidemiol*. Dec 2002;31(6):1253-62; discussion 1262-64. doi:10.1093/ije/31.6.1253
127. Velagaleti RS, Pencina MJ, Murabito JM, et al. Long-term trends in the incidence of heart failure after myocardial infarction. *Circulation*. Nov 11 2008;118(20):2057-62. doi:10.1161/circulationaha.108.784215
128. Saposnik G, Hill MD, O'Donnell M, Fang J, Hachinski V, Kapral MK. Variables associated with 7-day, 30-day, and 1-year fatality after ischemic stroke. *Stroke*. Aug 2008;39(8):2318-24. doi:10.1161/strokeaha.107.510362
129. D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. *Am Heart J*. Feb 2000;139(2 Pt 1):272-81. doi:10.1067/mhj.2000.96469
130. Andersen MN, Andersen KK, Kammersgaard LP, Olsen TS. Sex differences in stroke survival: 10-year follow-up of the Copenhagen stroke study cohort. *J Stroke Cerebrovasc Dis*. Sep-Oct 2005;14(5):215-20. doi:10.1016/j.jstrokecerebrovasdis.2005.06.002
131. de Kat AC, Dam V, Onland-Moret NC, Eijkemans MJ, Broekmans FJ, van der Schouw YT. Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. *BMC Med*. Jan 4 2017;15(1):2. doi:10.1186/s12916-016-0762-8
132. Lee KN, Na JO, Choi CU, et al. Prevalence and characteristics of resistant hypertension at primary clinics in Korea: a nationwide cross-sectional study. *Clin Hypertens*. 2015;22:4. doi:10.1186/s40885-016-0043-z
133. Abbasi A, Bakker SJ, Corpeleijn E, et al. Liver function tests and risk prediction of incident type 2 diabetes: evaluation in two independent cohorts. *PLoS One*. 2012;7(12):e51496. doi:10.1371/journal.pone.0051496
134. Boersma P, Villarroel M, Vahratian A. Heavy drinking among US adults, 2018. *NCHS Data Brief*. 2020;(374)
135. Moonesinghe R, Yang Q, Zhang Z, Khoury MJ. Prevalence and Cardiovascular Health Impact of Family History of Premature Heart Disease in the United States: Analysis of the National Health and Nutrition Examination Survey, 2007-2014. *J Am Heart Assoc*. Jul 16 2019;8(14):e012364. doi:10.1161/jaha.119.012364
136. Bhatt H, Gamboa CM, Safford MM, Soliman EZ, Glasser SP. Is there an association between the prevalence of atrial fibrillation and severity and control of hypertension? The REasons for Geographic And Racial Differences in Stroke study. *J Am Soc Hypertens*. Jul 2016;10(7):578-586.e5. doi:10.1016/j.jash.2016.05.007
137. Enright PL, Adams AB, Boyle PJ, Sherrill DL. Spirometry and maximal respiratory pressure references from healthy Minnesota 65- to 85-year-old women and men. *Chest*. Sep 1995;108(3):663-9. doi:10.1378/chest.108.3.663

138. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. Sep 16 2006;368(9540):1005-11. doi:10.1016/s0140-6736(06)69208-8
139. Sigurdsson E, Thorgeirsson G, Sigvaldason H, Sigfusson N. Prognostic role of cardiovascular risk factors for men with cardiomegaly (the Reykjavik Study). *Am J Cardiol*. Dec 15 1996;78(12):1355-61. doi:10.1016/s0002-9149(96)00650-9
140. Václavík J, Sedlák R, Jarkovský J, Kociánová E, Táborský M. Effect of spironolactone in resistant arterial hypertension: a randomized, double-blind, placebo-controlled trial (ASPIRANT-EXT). *Medicine (Baltimore)*. Dec 2014;93(27):e162. doi:10.1097/md.0000000000000162
141. Laurell K, Gustafsson S, Lampa E, et al. Persistence to antihypertensive drug classes in uncomplicated hypertension: a nationwide Swedish cohort study. *EClinicalMedicine*. Jan 2026;91:103696. doi:10.1016/j.eclinm.2025.103696
142. Elshahat A, Mansour A, Ellabban M, et al. Comparative effectiveness and safety of eplerenone and spironolactone in patients with heart failure: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. Sep 13 2024;24(1):489. doi:10.1186/s12872-024-04103-7
143. McKenna C, Walker S, Lorgelly P, et al. Cost-effectiveness of aldosterone antagonists for the treatment of post-myocardial infarction heart failure. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. May 2012;15(3):420-8. doi:10.1016/j.jval.2012.01.004
144. Koeche C, Nogueira ACC, Amaral G, et al. Cost-Effectiveness of Mineralocorticoid Receptor Antagonists in Ischemic and Nonischemic Heart Failure With Reduced Ejection Fraction: Perspective From a Universal Healthcare System. *Value Health Reg Issues*. May 2025;47:101084. doi:10.1016/j.vhri.2025.101084
145. Bounthavong M, Butler J, Dolan CM, et al. Cost-Effectiveness Analysis of Patiromer and Spironolactone Therapy in Heart Failure Patients with Hyperkalemia. *Pharmacoeconomics*. Dec 2018;36(12):1463-1473. doi:10.1007/s40273-018-0709-3
146. Ademi Z, Pasupathi K, Liew D. Cost-Effectiveness of Eplerenone Compared to Usual Care in Patients With Chronic Heart Failure and NYHA Class II Symptoms, an Australian Perspective. *Medicine (Baltimore)*. May 2016;95(18):e3531. doi:10.1097/md.0000000000003531
147. Johnson BH, Bonafede MM, Watson C. Short- and longer-term health-care resource utilization and costs associated with acute ischemic stroke. *Clinicoecon Outcomes Res*. 2016;8:53-61. doi:10.2147/ceor.S95662
148. Kazi DS, Elkind MSV, Deutsch A, et al. Forecasting the Economic Burden of Cardiovascular Disease and Stroke in the United States Through 2050: A Presidential Advisory From the American Heart Association. *Circulation*. Jul 23 2024;150(4):e89-e101. doi:10.1161/cir.0000000000001258
149. Kazi DS, Penko J, Coxson PG, Guzman D, Wei PC, Bibbins-Domingo K. Cost-Effectiveness of Alirocumab: A Just-in-Time Analysis Based on the ODYSSEY Outcomes Trial. *Ann Intern Med*. Feb 19 2019;170(4):221-229. doi:10.7326/m18-1776
150. Cowper PA, Knight JD, Davidson-Ray L, Peterson ED, Wang TY, Mark DB. Acute and 1-Year Hospitalization Costs for Acute Myocardial Infarction Treated With Percutaneous Coronary Intervention: Results From the TRANSLATE-ACS Registry. *J Am Heart Assoc*. Apr 16 2019;8(8):e011322. doi:10.1161/jaha.118.011322
151. Kazi DS, Moran AE, Coxson PG, et al. Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease. *Jama*. Aug 16 2016;316(7):743-53. doi:10.1001/jama.2016.11004

152. Urbich M, Globe G, Pantiri K, et al. A Systematic Review of Medical Costs Associated with Heart Failure in the USA (2014-2020). *Pharmacoeconomics*. Nov 2020;38(11):1219-1236. doi:10.1007/s40273-020-00952-0
153. American Heart Association & American Stroke Association. Cardiovascular disease: A costly burden for America. Projections through 2035. Accessed August 2, 2026, https://www.heart.org/-/media/files/get-involved/advocacy/burden-report-consumer-report.pdf
154. Heidenreich PA, Fonarow GC, Opsha Y, Sandhu AT, Sweitzer NK, Warraich HJ. Economic Issues in Heart Failure in the United States. *J Card Fail*. Mar 2022;28(3):453-466. doi:10.1016/j.cardfail.2021.12.017
155. Moyneur E, Bookhart BK, Mody SH, Fournier AA, Mallett D, Duh MS. The economic impact of pre-dialysis epoetin alpha on health care and work loss costs in chronic kidney disease: an employer's perspective. *Dis Manag*. Feb 2008;11(1):49-58. doi:10.1089/dis.2008.111715
156. Ebinger JE, Kauko A, Bello NA, Cheng S, Niiranen T. Apparent treatment-resistant hypertension associated lifetime cardiovascular risk in a longitudinal national registry. *Eur J Prev Cardiol*. Aug 1 2023;30(10):960-968. doi:10.1093/eurjpc/zwad066

Supplemental Material

A. Background: Supplemental Information

A1. Definitions

Blood pressure (BP): The force of circulating blood pushing against artery walls.[93] A reading is recorded using two numbers:

- **Systolic Blood Pressure (SBP)**: Blood pressure when the heart muscle contracts (systole). This is the first/upper number of a reading.[93]
- **Diastolic Blood Pressure (DBP):** Blood pressure while the heart muscle relaxes (diastole). This is the second/lower number of a reading.[93]

In standard clinical practice, a cuff and stethoscope are commonly used to measure blood pressure.[94] In clinical trials, there are various methods to measure blood pressure:

- **Automated Office Blood Pressure Monitoring (AOBP)**: A method of measuring blood pressure in a clinical setting using an automated device that obtains multiple BP readings, 30-60 seconds apart after a 3–5-minute rest. The measurements are taken while a patient is sitting and resting and may be attended or unattended.[95]
- **24-Hour Ambulatory Blood Pressure Monitoring (ABPM)**: A method of measuring blood pressure over a 24-hour period using an automated cuff device that obtains BP readings at set intervals during the day and night (i.e., every 15-30 minutes). Typically, this results in 40-60 BP measurements throughout a 24-hour period. Because it provides a 24-hour picture of blood pressure and has been most strongly associated with risk for major cardiovascular events, ABPM is regarded as the gold standard for BP measurement.[96]
- **Home Blood Pressure Monitoring (HBPM)**: A method of measuring blood pressure at home using an automated device while sitting and resting, as instructed by the individual's provider. Readings are typically obtained at least once daily over several days, which can be repeated as needed (e.g., monthly) to assess blood pressure outside of a clinical setting and guide long-term blood pressure management.[96]

Hypertension (High Blood Pressure): A common chronic condition, affecting nearly half of adults in the United States, defined clinically by a blood pressure consistently greater than or equal to 130/80 mm Hg (millimeters of mercury).[4,5]

- **Resistant Hypertension**: Blood pressure that remains uncontrolled (≥130/80 mm Hg) despite the use of ≥3 antihypertensive treatments at maximally tolerated doses including an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and a thiazide diuretic. Resistant hypertension also includes blood pressure that is at goal with ≥4 antihypertensive medications.[4]

Estimated Glomerular Filtration Rate (eGFR): An indirect estimate of the "rate at which the glomerulus filters plasma to produce an ultrafiltrate" to assess the overall function of the kidney. A decline in eGFR can be correlated with the loss of other functions in the kidney and is crucial to the management of chronic kidney disease.[97]

Chronic Kidney Disease (CKD): A chronic condition in which kidneys show signs of damage (e.g., increase in creatinine and/or presence of albumin in the urine) for ≥3 months. It is diagnosed and monitored with an eGFR or urine albumin-to-creatinine ratio (UACR) test. Hypertension is a major risk factor for CKD, and CKD also increases the risk of serious conditions such as heart disease and stroke. More than one in seven US adults have CKD, yet nine in 10 are unaware they have it.[98,99]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[100] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[101,102] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on

unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

An estimated 120 million or 48.1% of US adults live with hypertension. Table A1.1 provides estimates of hypertension by race/ethnicity among US adults using data from the Center for Disease Control's 2023 Hypertension Cascade Data.[5]

The prevalence of hypertension was the highest in Non-Hispanic Black Americans (57.8%), and this group may benefit 1.2 times more than the overall population from access to effective blood pressure medications.

Table A1.1. Health Improvement Distribution Index Estimates for Adults with Hypertension, 2017-2020[5]

Race/Ethnicity	Subgroup Estimate, %	Population Estimate, %	Subgroup Health Improvement Distribution Index
Non-Hispanic White	48.9	48.1	1.02
Non-Hispanic Black	57.8		1.20
Non-Hispanic Asian	45.2		0.94
Hispanic	38.6		0.80
Other	51.0		1.06

A2. Potential Cost-Saving Measures in Hypertension

ICER includes in its report's information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by baxdrostat and lorundrostat (e.g., reduced need for emergency care for hyperkalemia), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of hypertension beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient. No suggestions were received.

A3. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients.

ICER did not receive any feedback on this inquiry.

B. Patient and Other Stakeholder Perspectives: Supplemental Information

B1. Patient Community Input: Methods

We interviewed two patient advocacy organizations and one person living with hypertension about their experience with hypertension treatment and care. We also reviewed four submissions from patients living with hypertension to ICER's Share Your Story portal.

B2. Clinical Input: Methods

We spoke with five clinical experts with expertise in treating patients with hypertension, including two internists, two cardiologists, and one nephrologist. All worked at academic medical centers in the Eastern, Southern, and Western regions of the US.

C. Clinical Guidelines

2025 AHA / ACC / AANP / AAPA / ABC / ACCP / ACPM / AGS / AMA / ASPC / NMA / PCNA / SGIM Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults[4]

This joint guideline update from multiple specialty societies replaced a 2017 clinical practice guideline. The guideline defines hypertension as a blood pressure ≥130/80 mm Hg, and makes recommendations for evaluation and diagnosis of hypertension, including accurate measurement of blood pressure, laboratory tests and diagnostic procedures, and recommendations for screening for secondary forms of hypertension. The guideline also recommends the use of the American Heart Association's PREVENT risk calculator to estimate cardiovascular disease risk, and treatment recommendations are based on cardiovascular risk levels. The guideline gives recommendations on lifestyle modifications such as limiting sodium intake, managing stress, weight loss, healthy eating and physical activity. Recommendations for medication treatment include earlier initiation of medication for patients at higher cardiovascular risk, and initiation of two medications for patients with blood pressure ≥140/90 mm Hg. Recommended first-line medication classes include angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, long-acting dihydropyridine calcium channel blockers, and thiazide-type diuretics. Finally, there are recommendations for specific scenarios, including pregnancy and resistant hypertension.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Populations

We identified the following populations of interest:

- Adults with resistant hypertension who require an additional agent to reach their blood pressure goal, not on spironolactone, eplerenone, or amiloride
- Adults with uncontrolled hypertension despite use of two antihypertensive agents who do not tolerate a third first-line agent recommended by clinical guidelines
- Adults with uncontrolled hypertension despite use of two antihypertensive agents who have not been treated with a third first-line agent recommended by clinical guidelines

We evaluated the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors including age, sex, and race/ethnicity
- Baseline systolic blood pressure, body mass index, and kidney function (estimated glomerular filtration rate)

Interventions

- Baxdrostat (BAXFENDY™, AstraZeneca)
- Lorundrostat (Mineralys Therapeutics)

Comparators

We compared the agents to each other and to comparators based on population:

- For patients with resistant hypertension who require an additional agent to reach their blood pressure goal, we compared to:
    - Mineralocorticoid receptor antagonists (spironolactone or eplerenone)
    - Amiloride

- For patients with uncontrolled hypertension on two medications who did not tolerate a third first-line medication, we compared to:
    - Mineralocorticoid receptor antagonists (spironolactone or eplerenone)
    - Amiloride
- For patients on two medications who have uncontrolled hypertension and have not been started on a third first-line medication, we compared to:
    - Amlodipine

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Cardiovascular events (e.g., stroke, ischemic heart disease, heart failure, peripheral arterial disease)
    - Kidney events (e.g., end-stage kidney disease)
    - Mortality
    - Cognitive outcomes (e.g., dementia, Alzheimer's disease, mild cognitive impairment)
    - Quality of life
    - Tolerability and adverse events including:
        - Gynecomastia
        - Erectile dysfunction
        - Serious adverse events
- Other Outcomes
    - Hypertensive retinopathy
    - Reduction in blood pressure
    - Asymptomatic chronic kidney disease
    - Proteinuria
    - Other adverse events including:
        - Hyponatremia (low sodium)
        - Hyperkalemia (elevated potassium)

Timing

Evidence on intervention effectiveness and harms was derived from studies of at least four weeks duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the United States.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		

Section and Topic	Item #	Checklist Item
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on baxdrostat and lorundrostat for the treatment of uncontrolled or resistant hypertension followed established best research methods.[103,104] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[105] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms. We conducted an additional targeted literature search on the clinical evidence of amlodipine as a third agent for hypertension (Tables D1.4 and D1.5). We also looked for evidence on amlodipine when used in other lines of therapy (e.g., first-line therapy, dual versus triple therapy combinations, etc.).

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews).

Table D1.2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	exp Hypertension/
2	(“Hypertension” OR "Blood Pressure, High" OR "Blood Pressures, High" OR "High Blood Pressure" OR "High Blood Pressures" OR “Uncontrolled Hypertension” OR "Hypertension Resistant to Conventional Therapy" OR "Resistant Hypertension").ti,ab.
3	1 OR 2
4	("Lorundrostat" OR "Baxdrostat").ti,ab.
5	("Verospirone" OR "Spirolactone" OR "Veroshpiron" OR "Aldactone" OR "Aldactone A" OR "SC-9420" OR "SC9420" OR "SC 9420" OR "Spirolang" OR "Aquareduct" OR "Duraspiron" OR "Espironolactona Alter" OR "Espironolactona Mundogen" OR "Flumach" OR "Frumikal" OR "Jenaspiron" OR "Novo-Spiroton" OR "NovoSpiroton" OR "Novo Spiroton" OR "Practon" OR "Spiractin" OR "Spiro L.U.T." OR "Spiro Von Ct" OR "Spirobeta" OR "Spirogamma" OR "Spironone" OR "Spirospare" OR "Verospiron" OR "Spirono-Isis" OR "Spirono Isis" OR "Spironolactone" OR "Eplerenone" OR "Eplerenon" OR "Inspra").ti,ab.
6	("Amiloride" OR "Amiloride Hydrochloride" OR "Hydrochloride, Amiloride" OR "Amiloride Hydrochloride, Anhydrous" OR "Anhydrous Amiloride Hydrochloride" OR "Hydrochloride, Anhydrous Amiloride" OR

	"Midamor" OR "Modamide" OR "Amidal" OR "Amiduret Trom" OR "Amiloberag" OR "Kaluril" OR "Midoride").ti,ab.
7	3 and (4 OR 5 OR 6)
8	7 NOT (animals not (humans and animals)).sh.
9	8 NOT (addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).pt
10	limit 9 to English language
11	Remove duplicates from 10

Ran 4/16/2026

Table D1.3. Search Strategy of EMBASE

1	'hypertension'/exp
2	('arterial hypertension' OR 'blood pressure, high' OR 'high blood pressure' OR 'systemic hypertension' OR 'hypertension' OR 'drug resistant hypertension' OR 'intractable hypertension' OR 'medically refractory hypertension' OR 'pharmacotherapy resistant hypertension' OR 'recalcitrant hypertension' OR 'refractory hypertension' OR 'therapeutically resistant hypertension' OR 'therapy resistant hypertension' OR 'treatment resistant hypertension' OR 'resistant hypertension' OR 'uncontrolled hypertension'):ti,ab
3	#1 OR #2
4	('lorundrostat hydrobromide' OR 'mls 101' OR 'mls101' OR 'mt 4129' OR 'mt4129' OR 'lorundrostat' OR 'cin 107' OR 'cin107' OR 'ro 6836191' OR 'ro6836191' OR 'baxdrostat'):ti,ab
5	('sas 1060' OR 'sas1060' OR 'sc 9420' OR 'sc9420' OR 'spiractin' OR 'spiretic' OR 'spiridon' OR 'spirix' OR 'spiro' OR 'spiro ct' OR 'spirobene' OR 'spiroctan' OR 'spiroctan m' OR 'spirohexal' OR 'spirolacton' OR 'spirolactone' OR 'spirolang' OR 'spirolon' OR 'spiron' OR 'spirone' OR 'spironex' OR 'spirono-isis' OR 'spironol' OR 'spironolacton' OR 'spironolakton' OR 'spironone' OR 'spirothiobarbiturate 03620' OR 'spirotone' OR 'sth 14399' OR 'sth14399' OR 'supra puren' OR 'suprapuren' OR 'uractone' OR 'uractonum' OR 'urospir' OR 'verospiron' OR 'verospirone' OR 'xenalon' OR 'xenalon lactabs' OR 'youlactone' OR 'spironolactone' OR 'cgp 30 083' OR 'cgp 30083' OR 'cgp30083' OR 'elecor' OR 'epoxymexrenone' OR 'inspra' OR 'mexrenone, 9, 11alpha epoxy' OR 'sc 66110' OR 'sc66110' OR 'selara' OR 'eplerenone'):ti,ab
6	('amiclaran' OR 'amikal' OR 'amilo 5' OR 'amilorid' OR 'amiloride chloride' OR 'amiloride hcl' OR 'amiloride hydrochlorhydrate' OR 'amiloride hydrochloride' OR 'amiloride hydroxychloride' OR 'amiloridehydrochlorhydrate' OR 'amiloridine' OR 'amipramidine' OR 'amyloride' OR 'arumil' OR 'berkamil' OR 'colectril' OR 'guanamprazine' OR 'kaluril' OR 'medamor' OR 'midamor' OR 'mk 870' OR 'modamide' OR 'n amidino 3, 5 diamino 6 chloropyrazinamide' OR 'nirulid' OR 'pandiuren' OR 'amiloride'):ti,ab
7	#3 and (#4 OR #5 OR #6)
8	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
9	#7 NOT #8
10	#9 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
11	#10 AND [english]/lim
12	#11 NOT [medline]/lim

Ran 4/16/2026

Table D1.4. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials for Amlodipine in Uncontrolled Hypertension

1	exp Amlodipine/
2	("Uncontrolled Hypertension" or "essential hypertension" or "uncontrolled essential hypertension").ti,ab.
3	("Amlodipine" or "Norvasc" or "Amlor" or "Istin" or "Amlodipine Maleate" or "Amlodipine Besylate" or "Astudal" or "Amlodis").ti,ab.
4	1 and 2 and 3
5	4 not (animals not (humans and animals)).sh.
6	Randomized controlled trial/ or controlled clinical trial/ or randomization/ or double blind procedure/ or single blind procedure/ or crossover procedure/
7	(random$ or placebo$ or allocat$ or assign$ or trial$ or crossover$ or cross over$ or doubl$ blind$ or singl$ blind$).ti,ab.
8	6 or 7
9	5 and 8
10	Limit 9 to english language
11	Remove duplicates from 10

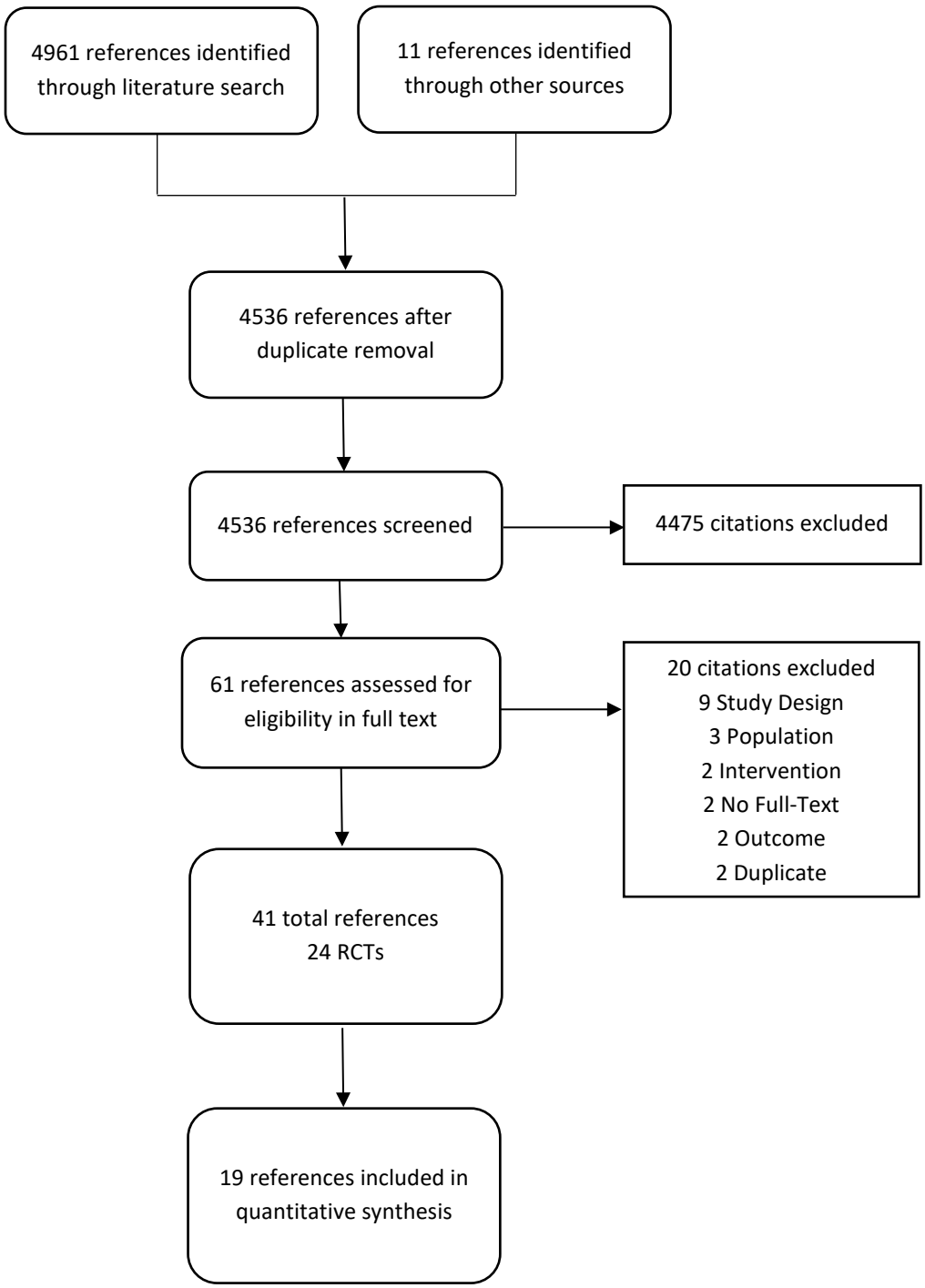
Ran 4/28/2026

Table D1.5. Search Strategy of EMBASE for Amlodipine in Uncontrolled Hypertension

1	'amlodipine'/exp
2	'uncontrolled hypertension':ti,ab OR 'essential hypertension':ti,ab OR 'uncontrolled essential hypertension':ti,ab
3	'amlodipine':ti,ab OR 'amloc':ti,ab OR 'amlodipin':ti,ab OR 'amlodipina':ti,ab OR 'amlopin':ti,ab OR 'drgt 119':ti,ab OR 'drgt119':ti,ab OR 'hgp 0904':ti,ab OR 'hgp0904':ti,ab OR 'stamlo':ti,ab OR 'uk 48340':ti,ab OR 'uk48340':ti,ab
4	#1 AND #2 AND #3
5	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
6	#4 NOT #5
7	'randomized controlled trial'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'crossover procedure'/exp
8	#6 AND #7
9	#8 AND [english]/lim
10	#9 NOT [medline]/lim

Ran 4/28/2026

Figure D1.1. PRISMA flow Chart Showing Results of Literature Search for Hypertension



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge; a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also reviewed FDA documents related to baxdrostat. These included the manufacturer's submission to the agency and FDA review documents. All literature that did not undergo a formal peer review process is described separately.

Data Extraction

Data was extracted into Microsoft Word and Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data was validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[104,106] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: "low risk of bias," "some concerns," or "high risk of bias." Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias in studies on the outcomes of changes in systolic blood pressure. See Table D1.6.

Table D1.6. Risk of Bias Assessment

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Baxdrostat						
BaxHTN	Low	Low	Low	Low	Low	Low
Bax24	Low	Low	Some Concerns	Low	Low	Some Concerns
	Comment: Of 217 randomized and treated: 89 baxdrostat and 95 placebo had valid ABPM at both timepoints. Missing/invalid data: 19 baxdrostat (18%) and 14 placebo (13%), a moderate proportion. The baxdrostat group had more treatment discontinuations due to adverse events (5% vs. 0%), which could introduce bias if those who discontinued had different BP responses. However, large magnitude of treatment effect (14 mm Hg) and sensitivity analyses mitigate this concern.					
BrigHTN	Low	Low	Low	Low	Low	Low
	Comment: Stopped after interim analysis for "overwhelming efficacy" by independent data monitoring committee. Planned final sample of 348 not reached, actual analyzed = 274 total patients. May slightly overestimate effect size but was pre-specified.					
FigHTN CKD	Low	Some Concerns	Some Concerns	Low	Low	Some Concerns
	Comment: A mid-study protocol amendment (changing potassium/sodium thresholds and titration rules) is a deviation that could affect safety assessments and potassium management, although less of concern for SBP outcome. 32% of participants did not complete treatment. However, the differential missingness between groups was modest (low-dose 18%, high-dose 19%, placebo 20% discontinued treatment).					
Lorundrostat						
Launch-HTN	Low	Low	Low	Low	Low	Low
Advance-HTN	Low	Low	Low	Low	Low	Low
Target-HTN	Low	Low	Low	Low	Low	Low
Spironolactone						
PATHWAY-2	Low	Low	Some Concerns	Low	Some Concerns	High
	Comment: As PATHWAY-2 was a crossover trial, bias was rated according to Cochrane Risk of Bias 2 tool for crossover trials. High risk on period and carryover effects (not reflected in table) due to no washout period in between treatment cycles. Some concerns regarding the handling of missing outcome data as it was assumed to be “Missing at Random”. Registration of the trial design on ClinicalTrials.gov (2015-02-15) occurred after study start (2009-05); potential for selective reporting of outcomes.					
ASPIRANT-EXT	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
	Comment: The study uses a per-protocol analysis rather than intention-to-treat and reports no missing data imputation or sensitivity analyses, although the low dropout rate (6.8%) is low. The trial was also an extension of a prematurely stopped trial. However, outcomes match research protocol.					
Oxlund 2013	Low	Low	Low	Low	Low	Low
Ni 2014	Some Concerns	Some Concerns	Low	Low	Some Concerns	Some Concerns
	Comment: No details on randomization method or allocation concealment procedures, or registered protocol in English language. Despite double-blind and intention to treat analysis, dose adjustments based on BP response could differentially affect results, potentially introducing confounding.					
Spironolactone vs. Amiloride						
SPARE	Low	Some Concerns	Low	High	Low	High
	Comment: High risk of bias due to the open-label trial design. Although participants were randomized, both participants and trial personnel were aware of the assigned interventions throughout the study. Even though the endpoint evaluation was blinded, this does not adequately mitigate the risk, because the primary outcome (home-measured SBP) was self-recorded on paper by unblinded participants. The initial dosages of spironolactone (12.5 mg) and amiloride (5 mg) could be doubled after four weeks of treatment at investigators' discretion if meeting SBP measurement and serum potassium thresholds.					
Eplerenone						
Karns 2012	Low	Low	Some Concerns	Low	Low	Some Concerns
	Comment: 29 of 155 participants (18.7%) discontinued the study due to protocol deviations and withdrawal of consent, with small number of patients per study arm. The primary analysis used LOCF to handle missing data, which can introduce bias if missingness depends on outcome, though attrition was similar across groups.					
Eguchi 2016	Some Concerns	High	Some Concerns	Some Concerns	Low	High
	Comment: Open-label design (unblinded participants/staff). Lack of a placebo, which may cause unconscious behavioral changes (e.g., diet, salt intake, adherence) in the control group. The primary endpoint of this study was the reduction of home morning SBP, for which the lack of blinding is highly likely to introduce bias. Unclear how missing data is handled. 10 of 35 eplerenone-treated patients were low-dose (25 mg/day).					
Amiloride						
PATHWAY-3	Low	Low	Low	Low	Some Concerns	Some Concerns

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
	Comment: Some concerns due to unavailability of a statistical analysis plan, and therefore, prespecified analyses. The linked NCT in the paper (NCT00797862) does not correspond to the correct trial on ClinicalTrials.gov (NCT02351973). The correct listing was published after enrollment was complete.					
Amlodipine						
TRINITY	Low	Low	Some Concerns	Low	Low	Some Concerns
	Comment: Dropout varied by group: completion rates were 88.7% (OM/AML), 83.4% (OM/HCTZ), 82.3% (triple), and 85.3% (AML/HCTZ) The triple combination group had the highest discontinuation rate due to adverse events (4.0% vs. 1.0-2.1% in dual groups) Some concerns due to differential dropout and use of last observation carried forward approach, which can bias results if missingness is related to treatment effect.					
Rakugi 2015	Low	Low	Low	Low	Low	Low
Higaki 2017	Low	Low	Low	Low	Low	Low
Calhoun 2009	Low	Low	Low	Low	Low	Low
	Comment: Efficacy data from 1 site (12 randomly assigned patients) was excluded from all of the efficacy analyses because of the discovery of several protocol irregularities. Unlikely to have materially influenced results given the large study size (n=2,271) and use of Intention to Treat analysis.					

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical Trial Diversity Rating (CDR) Tool.[19] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.7. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence/incidence estimates,[5] using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.8 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.9.

Table D1.7. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity.

Table D1.8. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.9. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Results

We identified prevalence data for race/ethnicity, sex, and age for adults with hypertension in the United States from Table 1 of the Center for Disease Control's 2023 Hypertension Cascade Data accessed via Million Hearts®.[5] Prevalence data for US adults treated for uncontrolled hypertension yielded similar results.[5]

Table D1.10. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older Adults)
BaxHTN	Fair	Fair	Good
Bax24	Fair	Fair	Good
Launch-HTN	Fair	Good	Good

Table D1.10. presents the clinical trial diversity ratings on race/ethnicity, sex, and age (older adults) for the pivotal trials of baxdrostat and lorundrostat (BaxHTN, Bax24, and Launch-HTN). Table D1.11. presents the prevalence data, trial data, PDRR, and overall ratings for each demographic category and trial.

Race/ethnicity: All trials received a "fair" rating for race and ethnicity due to an underrepresentation of Black/African American participants in the BaxHTN and Bax24 trials, and an underrepresentation of Asian participants in the Launch-HTN trial. All three trials were multinational with enrollment across North and South America, Asia, Europe, South Africa and Australia. As US-specific enrollment data were neither publicly available nor provided by the manufacturer, each trial was rated using the full sample.

Sex: The Launch-HTN trial received a "good" diversity rating for sex, whereas the baxdrostat trials received a "fair" diversity rating due to an underrepresentation of females.

Age: All trials received a "good" diversity rating for the representation of older adults (≥65 years).

Table D1.11. Race and Ethnicity, Sex, and Age

	Race/Ethnicity							Sex			Age	
	White	**Black/ AA**	**Asian**	**Hispanic/ Latino**	**AIAN**	**NHPI**	**Total Score**	**Male**	**Female**	**Total Score**	**≥65 Years**	**Total Score**
Prevalence[5]	76.76%	16.34%	5.92%	15.33%	NR	NR	-	52.11%	47.89%	-	27.73%	-
BaxHTN[20,21]	62.97%	7.43%	26.32%	13.10%	NR	NR	-	62.22%	37.78%	-	43.07%	-
PDRR	0.82	0.45	4.45	0.85	NC	NC	-	1.19	0.79	-	1.55	-
Score	3	1	3	3	NC	NC	10	3	2	5	3	-
Overall rating	Fair							Fair			NC	
Bax24[22]	78.34%	4.61%	16.13%	21.20%	NR	NR	-	64.52%	35.48%	-	29.03%	-
PDRR	1.02	0.28	2.72	1.38	NC	NC	-	1.24	0.74	-	1.05	-
Score	3	1	3	3	NC	NC	10	3	2	5	3	3
Overall rating	Fair							Fair			Good	
Launch-HTN[23]	67.68%	28.72%	2.22%	36.38%	NR	NR	-	53.09%	46.91%	-	41.18%	-
	0.88	1.76	0.38	2.37	NC	NC	-	1.02	0.98	-	1.49	-
Score	3	3	1	3	NC	NC	10	3	3	6	3	3
Overall rating	Fair							Good			Good	

AA: African American, AIAN: American Indian or Alaskan Native, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, NR: Not Reported, PDRR: Participant to Disease-prevalence Representation Ratio.

PDRR ≥0.8 indicates adequate representation.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[107,108]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for baxdrostat and lorundrostat and other therapies in our scope using ClinicalTrials.gov. Search terms included therapies identified in lines four to six to seven of Tables D1.2 and D1.3 and line three of Tables D1.4 and D1.5 of the literature searches (e.g., baxdrostat, lorundrostat, spironolactone, eplerenone, amiloride, amlodipine).

We identified a Phase II trial, HALO, that investigated baxdrostat at daily doses of 0.5 mg, 1 mg, and 2 mg in patients with uncontrolled hypertension. In this study, none of the baxdrostat doses significantly reduce SBP compared with placebo. Several hypotheses have been proposed to explain the lack of treatment effect, including an unexpectedly large placebo response and low medication adherence observed at certain study sites. Although the HALO trial results have not yet been published in a peer-reviewed journal, they were presented at the 2023 American College of Cardiology Annual Scientific Session and are available on ClinicalTrials.gov (NCT05137002).[109,110] HALO allowed patients who were hypertensive despite taking one drug, which did not fit our NMA inclusion criteria, and was excluded.

D2. Data Synthesis and Statistical Analyses

Feasibility of Conducting Indirect Comparison / Network Meta-Analysis (NMA)

We evaluated the feasibility of conducting an NMA to indirectly compare baxdrostat with lorundrostat, as well as each drug against our prespecified comparators (spironolactone, eplerenone, amiloride, and amlodipine). A total of 19 trials associated with these interventions were assessed for heterogeneity in study populations, study design, intervention type, outcome definitions and measurements, analytic methods, and study quality/risk of bias. We deemed these trials sufficiently similar in Population 1 and 3 of our scope. We did not identify relevant trials fitting our Population 2 criteria.

All data analyses were validated by an independent research team member. This process included reviewing and confirming the data analysis methods, data format, and analysis code. The member also re-ran the analysis, validated the results, and confirmed the appropriateness of the reported data.

NMA Methods

Baxdrostat and lorundrostat were compared against one another and against spironolactone, eplerenone, and amiloride for the Population 1 NMA and against amlodipine in the Population 3 NMA. Dosage information for each drug, including in-trial regimens and FDA-labeled doses, is outlined in Table D2.1.

Table D2.1. Dosage Information of Interventions in Network Meta-Analysis

Intervention	Dosage
Baxdrostat	Clinical trial dosage: 1-2 mg once daily FDA label recommended dosage: 2 mg once daily (or 1 mg for patients at increased risk for hyperkalemia or hyponatremia)
Lorundrostat	Clinical trial dosage: 50-100 mg once daily FDA label recommended dosage: NA
Spironolactone	Clinical trial dosage: 12.5 to 50 mg once daily FDA label recommended dosage: 25, 50 and 100 mg once daily
Eplerenone	Clinical trial dosage: 25 to 50 mg once daily, or 50 mg twice daily FDA label recommended dosage: 25 to 50 mg once daily, or 50 mg twice daily
Amiloride	Clinical trial dosage: 5 to 10 mg once daily FDA label recommended dosage: 5 to 10 mg once daily
Amlodipine	Clinical trial dosage: 5 to 10 mg once daily FDA label recommended dosage: 5 to 10 mg once daily
Placebo/ No Additional Pharmacological Treatment	Note: All trials allowed for the continuation of background antihypertensive therapy or underwent a washout or run-in period.

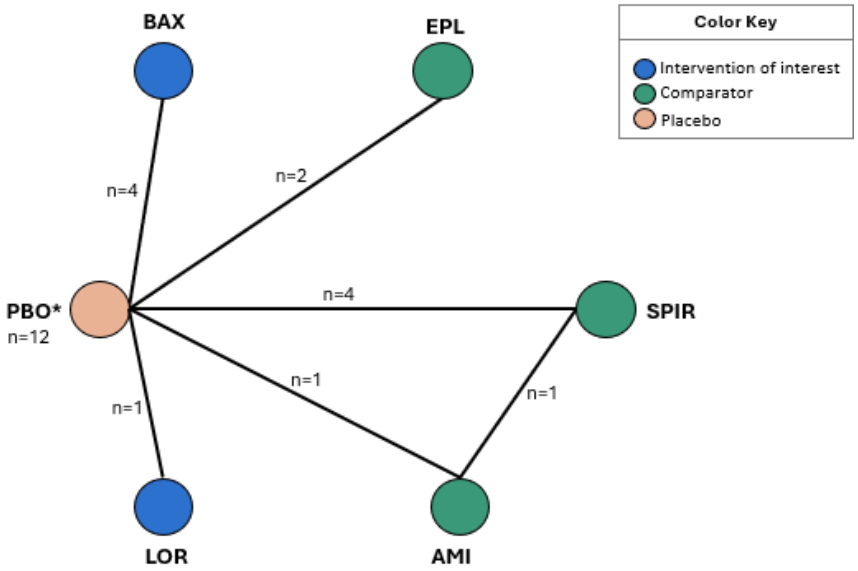
FDA: US Food and Drug Administration, mg: milligrams, NA: not applicable

We included RCTs in the NMA that were aligned with the inclusion/exclusion criteria of the pivotal trials of baxdrostat (BaxHTN) and lorundrostat (Launch-HTN). Eligible studies were RCTs that enrolled adults diagnosed with hypertension not controlled with three or more medications (Population 1) or with two medications (Population 3). The study duration of trials in the network ranged from six to 26 weeks. Due to data availability, we included several open-label studies (SPARE, Eguchi 2016) and one crossover trial (PATHWAY-2), while single-arm studies were excluded.

A total of 19 RCTs met our inclusion criteria (Figures D2.1, D2.2, and Table D2.2). Not all trials contributed to every NMA outcome; data availability for each trial is noted in the "NMA Contribution" column. Across study arms, participants were predominantly older adults in their 50s and 60s, mostly male, and had a baseline SBP in the 140s mm Hg despite treatment with two or more antihypertensive medications.

Both NMAs were conducted using R Studio in R Statistical Software (version 4.2.1). The primary outcome was mean change from baseline in SBP, a continuous outcome analyzed with a normal likelihood and identity link. Analyses were based on burn-in and sampling of 40,000 iterations and were analyzed using a random-effects Bayesian NMA. We conducted fixed-effects models to confirm model choice (Table D2.3).

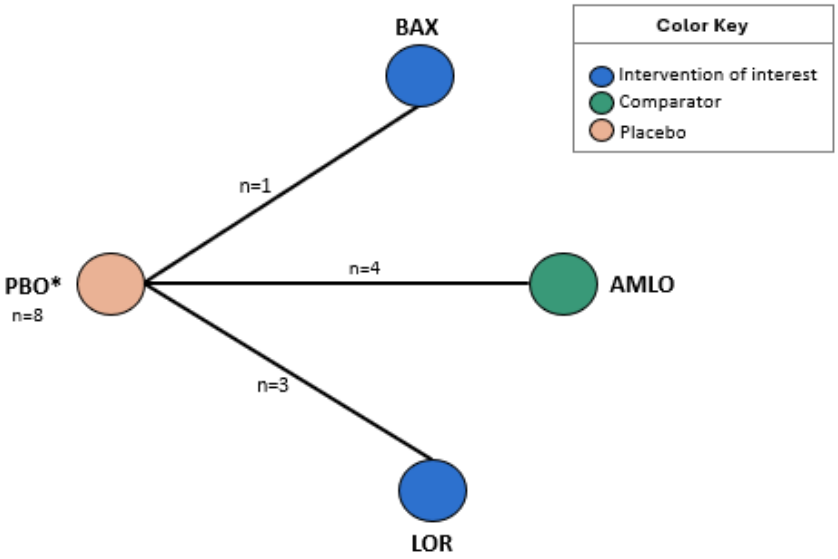
Figure D2.1. NMA Network Diagram for Resistant Hypertension Population (On ≥3 AHTs) (N=13)



AHTs: antihypertensives, AMI: amiloride, BAX: baxdrostat, EPL: eplerenone, LOR: lorundrostat, n: number, NMA: network meta-analysis, PBO: placebo, SPIR: spironolactone

*One eplerenone study and one amiloride study were compared against standard AHTS, and considered as versus placebo (i.e., background therapy of ≥3 AHTs) for our NMA.

Figure D2.2. NMA Network Diagram for Uncontrolled Hypertension Population (On 2 AHTs) (N=8)



AHTs: antihypertensives, AMLO: amlodipine, BAX: baxdrostat, LOR: lorundrostat, n: number, NMA: network meta-analysis, PBO: placebo

*All four amlodipine studies assessed triple combination therapy (with amlodipine) versus dual therapy (standard AHTs), and considered as versus placebo (i.e., background therapy of two AHTs) for our NMA.

Table D2.2. Hypertension NMA Trials Baseline Characteristics (N=19)

Study	Arm	n	Age, Mean (SD/Range)	Female, n (%)	SBP, Mean (SD)	# of AHTs, n (%)	eGFR, Mean (SD/Range)	NMA Contribution
Baxdrostat								
BaxHTN[20]	BAX 2 mg	266	61.8 (11.7)	103 (38.7)	AOBP: 149.1 (9.1)	Two: 67 (25.2) ≥Three: 199 (74.8)	84.3 (17.9)	Populations 1 and 3
	Placebo	264	61.9 (11.6)	102 (38.6)	AOBP: 149 (8.7)	Two: 71 (26.9) ≥Three: 193 (73.1)	84.1 (18)	
Bax24[22]	BAX 2 mg	108	60 (52-67)*	38 (35)	24h ABPM: 140.5 (8.4)	≥Three: 108 (100)	86.3 (18.1)	Population 1
	Placebo	109	61 (51-69)*	39 (36)	24h ABPM: 141.8 (11.8)	≥Three: 109 (100)	84.8 (19.5)	
BrigHTN[111]	BAX 2 mg	67	61.2 (10.8)	29 (43)	AOBP: 147.3 (11.8)	≥Three: 67 (100)	85.2 (19.4)	Population 1
	Placebo	69	63.8 (10.8)	27 (39)	AOBP: 148.9 (12.4)	≥Three: 69 (100)	85.5 (17.5)	
FigHTN CKD[37]	BAX 0.5-4 mg	129	67 (12)	44 (34)	AOBP: 150.9 (13.1)	Two: 31 (24) ≥Three: 81 (63)	45 (14)	Population 1
	Placebo	66	66 (11)	19 (29)	AOBP: 151.9 (13.1)	Two: 20 (30) ≥Three: 35 (53)	44 (15)	
Lorundrostat								
Launch-HTN[23]	LOR 50 mg	541	61.7 (10.6)	247 (45.7)	AOBP: 149 (12.2)	Two: 213 (39.4) ≥Three: 328 (60.6)	90.1 (17.8)	Populations 1 and 3
	Placebo	272	61.8 (10.4)	133 (48.9)	AOBP: 148.8 (12.2)	Two: 113 (41.5) ≥Three: 159 (58.5)	91.2 (16.4)	
Advance-HTN[50]	LOR 50 mg	94	61.3 (9.6)	38 (40)	AOBP: 141.8 (14.4)	Two: 59 (63) Three: 35 (37)	76.6 (17.8)	Population 3
	Placebo	95	59.1 (10.5)	33 (35)	AOBP: 141.7 (14)	Two: 61 (64) Three: 34 (36)	73.6 (18)	
Target-HTN[112]	LOR 50 mg	28	64.7 (9.5)	15 (53.6)	AOBP: 140 (12.1)	Two: 20 (71.4) ≥Three: 8 (28.6)	77.2 (14.1)	Population 3
	Placebo	30	62.6 (10.7)	17 (56.7)	AOBP: 142.9 (10.7)	Two: 17 (56.7) ≥Three: 13 (43.3)	81.6 (17.3)	
Spironolactone								
PATHWAY-2[†113]	SPIR/DOX/BIS/ PBO	335	61.4 (9.6)	105 (31)	HBPM: 147.6 (13.2)	≥Three: 335 (100)	91.1 (26.8)	Population 1
ASPIRANT-EXT[114]	SPIR 25 mg	74	60.4 (9.5)	24 (32.4)	24h ABPM: 144.5 (13.5)	≥Three: 74 (100)	NR	Population 1
	Placebo	76	59.7 (9.9)	28 (36.8)	24h ABPM: 141.2 (16.3)	≥Three: 76 (100)	NR	
SDHDS[31]	SPIR 25-50 mg	61	62.9 (7.1)	15 (25)	24h ABPM: 144 (9)	≥Three: 61 (100)	83 (55-128)*	Population 1
	Placebo	58	63.9 (6.9)	13 (22)	24h ABPM: 143 (11)	≥Three: 58 (100)	79 (56-137)*	

Study	Arm	n	Age, Mean (SD/Range)	Female, n (%)	SBP, Mean (SD)	# of AHTs, n (%)	eGFR, Mean (SD/Range)	NMA Contribution
Ni 2014[115]	SPIR 25-50 mg	40	55.7 (12.3)	16 (40)	24h ABPM: 147 (12.5)	≥Three: 40 (100)	NR	Population 1
	Placebo	36	54.9 (14.2)	15 (41.7)	24h ABPM: 145.5 (9.5)	≥Three: 36 (100)	NR	
Spironolactone vs. Amiloride								
SPARE[15]	SPIR 12.5-25 mg	60	55 (43-63)*	18 (30)	HBPM: 142.3 (8.5) [n=58]	≥Three: 60 (100)	93.1 (16)	Population 1
	AMI 5-10 mg	58	53 (44-69)*	17 (29.3)	HBPM: 141.5 (7.9) [n=56]	≥Three: 58 (100)	98.4 (12.3)	
Eplerenone								
Karns 2013[57]	EPL 100 mg	33	56.2 (7.7)	14 (42.4)	AOBP: 153.8 (8.9)	≥Three: 33 (100)	81.8 (14.5)	Population 1
	Placebo	33	59.8 (9.3)	11 (33.3)	AOBP: 153.4 (9.6)	≥Three: 33 (100)	76.9 (16.7)	
Eguchi 2016[42]	EPL 25-50 mg	35	60 (13)	10 (28.6)	24h ABPM: 134 (10)	≥Three: 35 (100)	NR	Population 1
	Control	22	65.9 (10.8)	11 (50)	24h ABPM: 136 (11)	≥Three: 22 (100)	NR	
Amiloride								
PATHWAY-3[48]	AMI/HCTZ 5-10/12.5-25 mg	133	61.5 (10.2)	63 (47.4)	AOBP: 156.2 (12.4)	NA‡	NR	Population 1
	HCTZ 25-50 mg	134	62.8 (9.9)	47 (35.1)	AOBP: 154.4 (11.7)	NA‡	NR	
Amlodipine								
TRINITY[116]	AMLO/OM/HCTZ 10/40/25 mg	627	54.7 (11.2)	307 (49)	AOBP: 167.9 (13.4)	NA‡	NR	Population 3
	OM/HCTZ 40/25 mg	637	55.9 (10.8)	298 (46.8)	AOBP: 169 (14.9)	NA‡	NR	
Rakugi 2015[117]	AMLO/Los/HCTZ 5/50/12.5 mg	141	53.9 (9.1)	33 (23.4)	Trough: 152 (10.2)	NA‡	NR	Population 3
	Los/HCTZ 50/12.5 mg	144	56.3 (9.8)	34 (23.6)	Trough: 151.5 (9.9)	NA‡	NR	
Higaki 2017[118]	AMLO/Tel/HCTZ 5/80/12.5 mg	68	56.1 (10.2)	13 (19.1)	AOBP: 145.2 (13.9)	Two: 68 (100)	NR	Population 3
	Tel/HCTZ 80/12.5 mg	64	54.4 (7.9)	15 (23.4)	AOBP: 141.5 (10.3)	Two: 64 (100)	NR	
Calhoun 2009[59]	AMLO/Val/HCTZ 10/320/25 mg	583	53.3 (10.3)	267 (45.8)	AOBP: 169.6 (14.5)	NA‡	NR	Population 3
	Val/HCTZ 320/25 mg	559	53.1 (10.4)	256 (45.8)	AOBP: 169.5 (13.8)	NA‡	NR	

ABPM: ambulatory blood pressure monitoring, AMI: amiloride, AMLO: amlodipine, AOBP: automated in-office blood pressure, BID: twice daily, BIS: bisoprolol, DOX: doxazosin, eGFR: estimated glomerular filtration rate, HBPM: home blood pressure monitoring, HCTZ: hydrochlorothiazide, LOS: losartan, n: number, NA: not applicable, NMA: network meta-analysis, NR: not reported, mg: milligrams, OM: Olmesartan, SBP: systolic blood pressure, SD: standard deviation,

SDHDS: South Danish Hypertension and Diabetes Study, SPIR: spironolactone, Tel: telmisartan, Val: valsartan, 24h: 24-hour
*Median (IQR)
†Baseline characteristics were reported for all randomized participants in PATHWAY-2 (a randomized crossover trial) who received four 12-week treatment cycles (spironolactone, doxazosin, bisoprolol, and placebo) for a total of 48 weeks.
‡Participants underwent a washout, placebo or dual combination therapy run-in period prior to receiving treatment.

Results

Results of the NMA are presented in Section 3.2 of the main report.

Assessing Model Fit

Random-Effects versus Fixed-Effects Model

Given the anticipated between-study heterogeneity in our network (i.e., differences in study duration, countries of enrollment, and SBP measurement), we decided *a priori* that random-effects model would be more appropriate for our base-case analysis. To validate this decision, we assessed model fit between the random-effects and fixed effect model for our two NMA outcomes. Based on the posterior distribution for the deviance (Dbar), the deviance information criterion (DIC), and heterogeneity (I^2), the random-effects model in the Population 1 NMA was justified. The same metrics showed similar fit in the Population 3 NMA.

Table D2.3. Random versus Fixed Effect Model Fit Assessment

Outcome	Data Points	Random Effects Model			Fixed Effects Model		
		Dbar	DIC	I^2	Dbar	DIC	I^2
Change in SBP (Population 1)	13	13.52	23.8	11%	28.36	33.34	58%
Change in SBP (Population 3)	8	6.14	11.04	0%	6.78	9.77	0%

Dbar: posterior distribution for the deviance, DIC: deviance information criterion, I^2: measure of heterogeneity, SBP: systolic blood pressure

League tables from the sensitivity analyses are shown below. Compared with the random-effects model, the fixed-effects model yielded narrower credible intervals for treatment comparisons. All statistically significant results were preserved in the fixed-effects analysis. In the Population 1 NMA, both baxdrostat versus placebo and spironolactone versus placebo point estimates reached statistical significance under the fixed-effects model.

POPULATION 1

Table D2.4. Mean Differences in Systolic Blood Pressure (mm Hg) (Random Effects – Base Case)

Baxdrostat					
-0.9 (-5.7, 3.8)	**Spironolactone**				
-2 (-10.1, 6.2)	-1.1 (-8.9, 6.9)	**Lorundrostat**			
-2.2 (-9.5, 5.5)	-1.3 (-8.3, 6.3)	-0.2 (-9.8, 9.9)	**Eplerenone**		
-4.4 (-10.6, 1.8)	-3.5 (-8.4, 1.6)	-2.4 (-11.3, 6.4)	-2.2 (-10.7, 5.8)	**Amiloride**	
-11 (-14.6, -7.3)	**-10.1 (-13.1, -6.8)**	**-9 (-16.3, -1.7)**	**-8.9 (-15.5, -2.4)**	**-6.6 (-11.5, -1.5)**	**Placebo**

Note: Each box represents the estimated treatment difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. N=13 studies. Therapies ranked by Surface Under the Cumulative RAnking (SUCRA) curve values.

Table D2.5. Mean Differences in Systolic Blood Pressure (mm Hg) (Fixed Effect – Sensitivity Analysis)

Baxdrostat					
-0.3 (-2.5, 2)	**Spironolactone**				
-2.3 (-7.1, 2.4)	-2.1 (-6.5, 2.4)	**Lorundrostat**			
-2.9 (-8.3, 2.5)	-2.7 (-7.7, 2.4)	-0.6 (-7.2, 6)	**Eplerenone**		
-4.4 (-7.4, -1.3)	**-4.1 (-6.5, -1.7)**	-2 (-7, 2.9)	-1.5 (-7, 4.1)	**Amiloride**	
-11.3 (-13.3, -9.3)	**-11.1 (-12, -10.1)**	**-9 (-13.3, -4.6)**	**-8.4 (-13.4, -3.4)**	**-7 (-9.3, -4.6)**	**Placebo**

Note: Each box represents the estimated treatment difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. N=13 studies. Therapies ranked by Surface Under the Cumulative RAnking (SUCRA) curve values.

POPULATION 3

Table D2.6. Mean Differences in Systolic Blood Pressure (mm Hg) (Random Effects – Base Case)

Baxdrostat			
-1.5 (-9, 5.7)	**Lorundrostat**		
-1.8 (-8.6, 4.8)	-0.3 (-4.6, 4.1)	**Amlodipine**	
-10.1 (-16.6, -3.9)	**-8.6 (-12.4, -4.8)**	**-8.3 (-10.7, -6.2)**	**Placebo**

Note: Each box represents the estimated treatment difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. N=8 studies. Therapies ranked by Surface Under the Cumulative RAnking (SUCRA) curve values.

Table D2.7. Mean Differences in Systolic Blood Pressure (mm Hg) (Fixed Effect – Sensitivity Analysis)

Baxdrostat			
-1.6 (-7.7, 4.6)	**Lorundrostat**		
-1.9 (-7.3, 3.4)	-0.4 (-3.7, 2.9)	**Amlodipine**	
-10.1 (-15.3, -4.9)	**-8.6 (-11.7, -5.4)**	**-8.1 (-9.3, -7)**	**Placebo**

Note: Each box represents the estimated treatment difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. N=8 studies. Therapies ranked by Surface Under the Cumulative RAnking (SUCRA) curve values.

Sensitivity Analysis

We conducted a sensitivity analysis which excluded three studies from our Population 1 NMA that we deemed to be at high risk of bias: SPARE, Eguchi 2016, and PATHWAY-2 (Table D2.8). This exclusion strengthened the point estimate for eplerenone versus placebo and elevated its rank against other treatments, albeit with wider credible intervals. The point estimate for amiloride versus placebo is no longer statistically significant.

Table D2.8. Mean Differences in Systolic Blood Pressure (mm Hg) (Random Effects – Exclusion of High Risk of Bias Studies)

Eplerenone					
-3.4 (-14.3, 7.1)	**Baxdrostat**				
-3.3 (-14.3, 7.2)	0.2 (-5.2, 5.2)	**Spironolactone**			
-5.5 (-18, 6.7)	-2.1 (-9.9, 6.1)	-2.3 (-10.1, 6.3)	**Lorundrostat**		
-10.6 (-22.6, 1.3)	-7.2 (-14.5, 0.6)	-7.5 (-14.6, 0.7)	-5.1 (-14.9, 4.8)	**Amiloride**	
-14.5 (-24.7, -4.5)	**-11.1 (-14.4, -7.4)**	**-11.4 (-14.7, -7)**	**-9 (-16.2, -1.8)**	-3.9 (-10.7, 2.7)	**Placebo**

Note: Each box represents the estimated treatment difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 0. N=10 studies. Therapies ranked by Surface Under the Cumulative RAnking (SUCRA) curve values.

NMA Input Data

The inputs abstracted and used in the NMA are provided in Tables D2.9 and D2.10.

Table D2.9. Input Data for NMA in Population 1: Change from Baseline in Systolic Blood Pressure (N=13)

Study	Treatment	Treatment Effect	Standard Error*	SBP Measurement	Source
BaxHTN	BAX	-9.8	1.71	AOBP	Figure 2: Flack et al., 2025
	PBO	NA	NA		
Bax24	BAX	-14	1.63	ABPM	Table 2: Azizi et al., 2026
	PBO	NA	NA		
BrigHTN	BAX	-11	2.78	AOBP	In-text page 400: Freeman et al., 2023
	PBO	NA	NA		
FigHTN CKD	BAX	-8.1	2.7	AOBP	In-text page 302: Dwyer et al., 2026
	PBO	NA	NA		
Launch-HTN	LOR	-9	2.21	AOBP	Table 2: Saxena et al., 2025
	PBO	NA	NA		
PATHWAY-2	SPIR	-9.85	0.89	HBPM	Supplementary table S4B: Williams et al, 2015
	PBO	NA	NA		
ASPIRANT-EXT	SPIR	-10.5	2.12	ABPM	Table 2: Václavík et al., 2014
	PBO	NA	NA		
SDHDS	SPIR	-8.9	2.19	ABPM	Table 3: Oxlund et al., 2013
	PBO	NA	NA		
Ni 2014	SPIR	-12.5	0.66	ABPM	Table 2: Ni et al., 2014
	PBO	NA	NA		
SPARE	SPIR	-0.68	1.72	HBPM	Table 2: Lee et al., 2025
	AMI	NA	NA		
Karns 2013	EPL	-14.7	4.29	ABPM	Table 2: Makai et al., 2017
	PBO	NA	NA		
Eguchi 2016	EPL	-5	3.16	ABPM	

Study	Treatment	Treatment Effect	Standard Error*	SBP Measurement	Source
	PBO	NA	NA		Table 2: Makai et al., 2017
PATHWAY-3	AMI	-3.9	1.63	AOBP	Table 3: Brown et al., 2016
	PBO	NA	NA		

AMI: amiloride, ABPM: ambulatory blood pressure monitoring, AOBP: automated in-office blood pressure, BAX: baxdrostat, CKD: Chronic Kidney Disease, EPL: eplerenone, HBPM: home blood pressure monitoring, HTN: hypertension, LOR: lorundrostat, n: number, PBO: placebo, SBP: systolic blood pressure, SPIR: spironolactone
*Standard error was calculated using the confidence intervals when not reported.

Table D2.10. Input Data for NMA in Population 3: Change from Baseline in Systolic Blood Pressure (N=8)

Study	Treatment	Treatment Effect	Standard Error*	SBP Measurement	Source
BaxHTN	BAX	-10.1	2.65	AOBP	Figure 2: Flack et al., 2025
	PBO	NA	NA		
Launch-HTN	LOR	-8.8	2.65	AOBP	Table 2: Saxena et al., 2025
	PBO	NA	NA		
Advance-HTN	LOR	-7.9	2.39	ABPM	Table 2: Laffin et al., 2025
	PBO	NA	NA		
Target-HTN	LOR	-9.6	3.77	AOBP	Table 2: Laffin et al., 2023
	PBO	NA	NA		
TRINITY	AMLO	-7.4	1.13	AOBP	Figure 3: Oparil et al., 2010
	PBO	NA	NA		
Rakugi 2015	AMLO	-10.3	1.3	Cuff and stethoscope	Table 2: Rakugi et al., 2015
	PBO	NA	NA		
Higaki 2017	AMLO	-8.6	2.7	ABPM	In-text page 56: Higaki et al., 2017
	PBO	NA	NA		
Calhoun 2009	AMLO	-7.6	0.85	AOBP	Table 2: Calhoun et al., 2009
	PBO	NA	NA		

ABPM: ambulatory blood pressure monitoring, AMLO: amlodipine, AOBP: automated in-office blood pressure, BAX: baxdrostat, HTN: hypertension, LOR: lorundrostat, n: number, PBO: placebo, SBP: systolic blood pressure
*Standard error was calculated using the confidence intervals when not reported.

NMA Limitations

- The SBP measurements in the studies of our two NMAs included a mix of 24-hour ambulatory, in-office, and at-home measurements. We opted to use best available estimate depending on factors such as sample size and time duration closest to 12 weeks. The 24-hour ambulatory blood pressure monitoring approach is regarded as the gold standard given its comprehensive capture of blood pressure control beyond the office setting, including overnight readings.[119]

- Several trials in the network had durations shorter than the 12-week period used in the pivotal studies, which could potentially underestimate the magnitude of SBP reduction for some treatments. However, this may not be a major concern, as supported by the ASPIRANT-EXT trial; the authors noted that although their study duration was only eight weeks, the maximal hypotensive effect of spironolactone in patients with resistant hypertension is achieved after seven weeks, suggesting that longer follow-up would not have yielded further BP reduction.[114]

- The Population 1 NMA was limited by a sparse network with just one head-to-head trial (SPARE), while the Population 3 NMA had no direct trials at all. This over-reliance on indirect evidence could make our comparative inferences less definitive than those derived from direct randomized comparisons.

- In order to include amiloride into the Population 1 network, we incorporated two studies, including an open-label Korean-only RCT (SPARE) comparing low dose spironolactone (12.5 to 25 mg; n=60) against 5 to 10 mg amiloride (n=58), and the PATHWAY-3 RCT which evaluated amiloride/hydrochlorothiazide versus hydrochlorothiazide alone in patients on average of 1.5 meds (9% were previously untreated). Both studies have limitations which limit our certainty around amiloride as a therapy for resistant hypertension.

    - The starting spironolactone dosage used in the SPARE trial (12.5 mg once daily) is lower than the recommended prescribed dose of 25 to 100 mg once daily, which could underestimate the magnitude of SBP reduction of spironolactone against amiloride in a treatment-resistant hypertension population. The open-label design of the trial also increases uncertainty around this comparison.

    - The PATHWAY-3 study did not evaluate amiloride as monotherapy. It is unknown as to whether there is any synergistic effect of amiloride as a pairing with hydrochlorothiazide, versus its effect as a single therapy added to an established three or more drug regimen.

- In our Population 3 NMA, the amlodipine studies did not follow a study design of amlodipine versus placebo in patients on two medications, as was the case with the baxdrostat and lorundrostat studies. The studies evaluated amlodipine as a component of a fixed-dose triple combination therapy compared with a dual combination that did not contain amlodipine. For example, one study compared the change in SBP at week eight between olmesartan (OM) 40 mg + amlodipine (AMLO) 10 mg + hydrochlorothiazide (HCTZ) 25 mg versus OM 40 mg + HCTZ 25 mg. This study design introduces uncertainty regarding whether amlodipine would produce a different magnitude of effect on SBP change if it were studied as monotherapy added to an established two-medication regimen, rather than as a component of a fixed-dose triple combination therapy.

- For studies that did not report subgroup data on change in SBP stratified by baseline medication count (two versus three plus medications), we assigned the study to the NMA population representing the majority of trial participants. For example, in the lorundrostat ADVANCE-HTN trial, 63% of participants were on two medications and 36% were on three or more medications. The available subgroup data for the two- and three-medication groups was limited to change in SBP at week four, which we considered too short a follow-up to be clinically meaningful. Instead, we used the 12-week change from baseline in SBP for the overall trial population in the Population 3 NMA (uncontrolled on two medications). We requested week 12 subgroup data by baseline medication count from both manufacturers. However, both declined to provide these data.

D3. Evidence Tables

Table D3.1. Study Design for All Studies

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
Baxdrostat				
BaxHTN (NCT06034743)[20]	Phase III, double-blind, randomized, placebo-controlled, parallel-arm trial followed by a 12-week open-label and an 8-week randomized withdrawal period. N=794	All arms were administered once daily for 12 weeks in the double-blind period following a two-week placebo run-in period. - 1 mg BAX (n=264) - 2 mg BAX (n=266) - Placebo (n=264)	Inclusion - Adults taking 2 AHTs and BP not at goal or ≥3 AHTs for rHTN, with ≥1 diuretic - AOBP SBP ≥140 to <170 mm Hg - eGFR ≥45 mL/min/1.73 m² - Serum potassium level ≥3.5 and <5 mmol/L Exclusion - Mean sitting AOBP SBP ≥170/110 mm Hg - Concomitant treatment with any MRAs, antiarrhythmic medications, or potassium-sparing diuretics - Had secondary hypertension or persistent atrial fibrillation - Cardiovascular or cerebrovascular events within ≥6 months	- Change from baseline in AOBP SBP and DBP at week 12, and at week 6 by subpopulations. - Proportion of those who achieve SBP <130 mm Hg at week 12. - Adverse events up to week 12.
Bax24 (NCT06168409)[22]	Phase III, randomized, double-blind, placebo-controlled, parallel-arm trial	All arms were administered once daily for 12 weeks in the double-blind period following a	Inclusion - Adults taking ≥3 AHTs, with ≥1 diuretic - AOBPM SBP ≥140 to <170	- Change from baseline in 24h ABPM, ABPM daytime/ nighttime, and AOBP SBP and DBP at week 12.

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
	N=217	two-week placebo run-in period. - 2 mg BAX (n=108) - Placebo (n=109)	mm Hg - eGFR ≥45 mL/min/1.73 m² - Serum potassium level ≥3.5 and <5 mmol/L Exclusion - Mean seated ABPM ≥170/110 mm Hg - Concomitant treatment with MRAs, antiarrhythmic medications, or potassium-sparing diuretics - Had uncontrolled diabetes, secondary HTN, or persistent atrial fibrillation - Cardiovascular or cerebrovascular events within ≥6 months	- Proportion of those who achieve AOBP SBP <130 mm Hg at week 12. - Adverse events up to week 14 (including 2-week run-in).
BrigHTN (NCT04519658)[111]	Phase II, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging trial. N=275	All arms were administered once daily for 12 weeks following a two-week placebo run-in period. - 0.5 BAX (n=69) - 1 mg BAX (n=70) - 2 mg BAX (n=67) - Placebo (n=69)	Inclusion - Adults taking ≥3 AHTs for ≥4 weeks, with ≥1 diuretic - Seated BP ≥130/80 mm Hg Exclusion - Seated BP ≥180/110 mm Hg - eGFR <45 mL/min/1.73 m² - Had uncontrolled diabetes - BMI >40 kg/m²	- Change from baseline in AOBP SBP and DBP at week 12. - Proportion of those who achieve BP <130/80 mm Hg at week 12. - Adverse events up to week 12.

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
			- Unwillingness/inability to discontinue an MRA or potassium-sparing diuretic	
FigHTN CKD (NCT05432167)[37]	Phase II, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging trial. N=195	All arms were administered once daily for 26 weeks following a two-week placebo run-in period. Doses could be increased after four weeks. - 0.5-1 mg BAX (n=65) - 2-4 mg BAX (n=64) - Placebo (n=66)	Inclusion - Adults taking an ACEi or ARB with a mean seated SBP ≥140 mm Hg and elevated UACR - Prior diagnosis of mild-to-severe CKD Exclusion - Seated BP >180/110 mm Hg - Had type 1 diabetes - Concomitant treatment with MRAs or potassium-sparing diuretic	- Change from baseline in AOBP SBP at week 26. - Change from baseline in eGFR at week 26. - Proportion of those who achieve SBP <130 mm Hg at week 26. - Treatment emergent adverse events up to week 26.
Lorundrostat				
Launch-HTN (NCT06153693)[23]	Phase III, double-blind, randomized, placebo-controlled, parallel-arm trial. N=1,083	All arms were administered once daily following a two-week placebo run-in period. - 50 mg LOR for 12 weeks (n=541) - 50 mg LOR for 6 weeks, then 100 mg LOR for 6 weeks if prespecified criteria met (n=270) - Placebo for 12 weeks (n=272)	Inclusion - Adults with HTN for ≥6 months and taking 2-5 AHT medications - AOBP SBP ≥135 to ≤ 180 mm Hg plus AOBP DBP ≥65 and ≤110 mm Hg, or AOBP DBP ≥90 and ≤110 mm Hg - BMI ≤18 kg/m^2 Exclusion - Treatment with MRAs, epithelium sodium channel inhibitors, and potassium-	- Change from baseline in AOBP SBP at week six, and by subpopulations. - Adverse events up to week 12.

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
			sparing diuretics ≥1 month of screening - eGFR <45 mL/min/1.73 m² - Serum potassium > 5.0 mmol/L at screening or > 4.8 mmol/L at randomization - Serum sodium <135 mmol/L at screening	
Advance-HTN (NCT05769608)[50]	Phase II, double-blind, randomized, placebo-controlled, parallel-arm trial. N=285	All arms were administered once daily following a three-week placebo run-in period. - 50 mg LOR for 12 weeks (n=94) - 50 mg LOR for 4 weeks, then 100 mg LOR for 8 weeks if prespecified criteria met (n=96) - Placebo for 12 weeks (n=95)	Inclusion - Adults taking 2-5 AHTs - AOBP SBP of 140-180 mm Hg and DBP of 65-110 mm Hg, or DBP of 90-110 mm Hg - 24h ABPM SBP of 130-180 mm Hg or DBP > 80 mm Hg - BMI 18-40 kg/m² Exclusion - eGFR <45 mL/min/1.73 m² - Serum potassium > 5.0 mmol/L - Serum sodium <135 mmol/L	- Change from baseline in 24h ABPM SBP at week 12, and at week 4 by subpopulations. - Change from baseline in AOBP SBP at week 12, with dose increase at week four. - Proportion of those who achieve SBP <125 mm Hg at week four and 12. - Adverse events up to week 12.
Target-HTN (NCT05001945)[112]	Phase II double-blind, randomized, placebo-controlled, dose-ranging trial. N=200	Treatment was for 8 weeks following a two-week placebo run-in period. Cohort 1 - LOR 100 mg daily (n=30) - LOR 50 mg daily (n=28) - LOR 12.5 mg daily (n=23)	Inclusion - Adults taking ≥2 AHTs - AOBP with SBP ≥130 mm Hg - Serum cortisol ≥18 mcg/dL Exclusion	- Change from baseline in AOBP and ABPM SBP and DBP at week eight. - Proportion of those who achieve BP <130/80 mm Hg at week 8. - Adverse events up to week eight.

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
		- LOR 25 mg BID (n=30) - LOR 12.5 mg BID (n=22) - Placebo (n=30) Cohort 2 - LOR 100 mg daily (n=31) - Placebo (n=6)	- Concomitant treatment with MRAs, ENaC inhibitors - eGFR <60 mL/min/1.73 m² - BP ≥175/100 mm Hg for Part 1 and BP 160/100 mm Hg for Part 2 - Had hyperkalemia, hypokalemia, orthostatic HTN, or type 1 diabetes	
Spironolactone				
PATHWAY-2 (NCT02369081)[113]	Phase IV, double-blind, randomized, placebo-controlled, crossover trial. N=314	Patients rotated through 12 weeks of once-daily treatment with each arm following a month's placebo run-in period. - Spironolactone 25-50 mg (n=285) - Doxazosin 4-8 mg (n=282) - Bisoprolol 5-10 mg (n=285) - Placebo (n=274)	Inclusion - Adults with rHTN (AOBP and HBPM SBP ≥130 mm Hg despite taking three AHTs for ≥3 months, including a diuretic) Exclusion - eGFR <45 mL/min/1.73 m² - Suspected non-adherence to AHT treatment - AOBP >200/120 mm Hg - Had secondary/accelerated HTN, type 1 diabetes, sustained atrial fibrillation, chronic illness, or recent cardiovascular hospitalization	- Between-treatment comparison of change from baseline in HBPM SBP from mid-cycle (week six) to end-of-cycle (week 12). - Adverse events by treatment arm (12-week cycle).
SPARE (NCT04331691)[15]	Phase IV, open-label, randomized, blinded end-point trial.	All arms were administered for 12 weeks once daily following a 4-week run-in period with a fixed-dose triple medication	Inclusion - Adults (19-75) with rHTN (AOBP SBP 130-180 mm Hg despite taking ≥3 AHTs)	- Within- and between-treatment comparison of change from baseline in HBPM SBP at week 12.

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
	N=118	combination (ACEi, CCB, thiazide diuretic). Doses could be increased to BID after 4 weeks if SBP ≥130 mm Hg and serum potassium <5 mmol/L. - Spironolactone 12.5-25 mg (n=60) - Amiloride 5-10 mg (n=58)	Exclusion - eGFR <50 mL/min/1.73 m² - Had hyperkalemia, liver disease, biliary obstruction, or gastrointestinal conditions - Had severe/ uncontrolled HTN, significant CVD, or any recent cardiovascular or cerebrovascular events	- Within- and between-treatment comparison of change from baseline in HBPM DBP at week 12.
ASPIRANT-EXT (NCT00524615)[114]	Phase IV, double-blind, randomized, placebo-controlled trial. N=160	All arms were administered once daily for 8 weeks in addition to current AHT regimen. - Spironolactone 25 mg (n=74) - Placebo (n=76)	Inclusion - Adults with rHTN (office BP >140/90 mm Hg despite taking ≥3 AHTs) - If office BP >130/80 mm Hg, patients with CKD or diabetes could be enrolled Exclusion - eGFR <40 mL/min/1.73 m² - Had severe or secondary HTN, kidney insufficiency, or hyponatremia - Prior use of MRAs	- Change from baseline in 24h ABPM, ABPM daytime/ nighttime, and AOBP SBP and DBP at week eight. - Change from baseline in laboratory values (e.g., serum potassium, sodium) at week eight.
SDHDS (NCT01062763)[31]	Phase III, double-blind, randomized, placebo-controlled trial. N=119	All arms were administered once daily for 16 weeks in addition to previous treatment. Doses could be increased to BID after four weeks if BP <130/80 mm Hg was not achieved.	Inclusion - Patients aged 30–74 years with type 2 diabetes and resistant hypertension (ABPM BP ≥130/80 mm Hg despite taking ≥3 AHTs)	- Change from baseline in AOBP, 24h ABPM, and ABPM daytime/nighttime SBP and DBP at week 16. - Adverse events up to week 16.

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
		- Spironolactone 25-50 mg (n=57) - Placebo (n=55)	- Treatment with antiglycemic treatment for ≥1 month Exclusion - Office BP >180/110 mm Hg, or ABPM daytime BP >170/85 mm Hg - Had secondary HTN, severe HF, cardiac arrhythmia, HbA1c >10%, severe dyslipidemia, or kidney insufficiency	
Ni 2014[115]	Prospective, double-blind, randomized, prospective trial. N=76	All arms were administered once daily for 12 weeks in addition to previous treatment. Doses could be increased after 4 weeks if clinical BP >135/85 mm Hg. - Spironolactone 25-50 mg (n=40) - Placebo (n=36)	Inclusion - Adults (aged ≥16 years) diagnosed with ESKD and undergoing stable dialysis for ≥3 months - Refractory HTN for ≥6 months despite taking ≥3 AHTs (predialysis BP >160/90 mm Hg, postdialysis BP >140/80 mm Hg, or peritoneal BP ≥140/90 mm Hg) Exclusion - Potassium level > 5 mmol/L	- Change from baseline in morning and 24h ABPM SBP and DBP at week 12. - Change from baseline in laboratory values (e.g., serum potassium, urine volume) at week 12.
Spironolactone vs. Amiloride				

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
SPARE (NCT04331691)[15]	Phase IV, open-label, randomized, blinded endpoint trial. N=118	All arms were administered for 12 weeks once daily following a four-week run-in period with a fixed-dose triple medication combination (ACEi, CCB, thiazide diuretic). Doses could be increased to BID after 4 weeks if SBP ≥130 mm Hg and serum potassium <5 mmol/L. - Spironolactone 12.5-25 mg (n=60) - Amiloride 5-10 mg (n=58)	Inclusion - Adults (19-75) with rHTN (AOBP SBP 130-180 mm Hg despite taking ≥3 AHTs) Exclusion - eGFR <50 mL/min/1.73 m^2 - Had hyperkalemia, liver disease, biliary obstruction, or gastrointestinal conditions - Had severe/ uncontrolled HTN, significant CVD, or any recent cardiovascular or cerebrovascular events	- Within- and between-treatment comparison of change from baseline in HBPM SBP at week 12. - Within- and between-treatment comparison of change from baseline in HBPM DBP at week 12.
Eplerenone				
Karns 2013 (NCT00817635)[57]	Phase II, double-blind, randomized, prospective, placebo- and active-controlled, parallel-group, dose-ranging trial. N=155	The eplerenone and placebo arms were of interest in our review and were administered for eight weeks following a two-week placebo run-in period. - Eplerenone 50 mg (n=33) - Osilodrostat 0.25 mg BID (n=32) - Osilodrostat 1 mg daily (n=26) - Osilodrostat 0.5/1 mg BID (n=31) - Placebo (n=33)	Inclusion - Adults with rHTN (i.e., failure to achieve BP goals despite taking ≥3 AHTs for ≥4 weeks) Exclusion - History of secondary HTN, or type 1 or type 2 diabetes - Treatment with aldosterone receptor antagonists, direct renin antagonists or potassium-sparing diuretics within four weeks of study - Recent history of significant cerebrovascular	- Change from baseline in AOBP, 24h ABPM, and ABPM daytime/nighttime SBP and DBP at week eight. - Change from baseline in RAAS biomarkers at week eight. - Adverse events up to 10 weeks (including two-week run-in).

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
			or CVD (e.g., HF, MI, stroke/TIA)	
Eguchi 2016[42]	Open-label, randomized, prospective, parallel-controlled trial. N=57	All arms were administered for 12 weeks following a 4-week observational period. - Eplerenone 25-50 mg in addition to AHTs (n=35) - Control group (AHTs) (n=22)	Inclusion - Adults (aged ≥20 years) with rHTN (HBPM morning SBP ≥135/80 mm Hg despite taking ≥3 AHTs) Exclusion - Hyperkalemia or serum potassium level >5 mEq/L - Hepatic damage or kidney deficiency - Use of spironolactone	- Change from baseline in AOBP, 24h ABPM, and HBPM SBP and DBP at week 12. - Change from baseline in laboratory values (e.g., serum potassium, sodium) at week 12.
Amiloride				
PATHWAY-3[48]	Phase IV, double-blind randomized, parallel-group trial. N=399	All arms were administered once daily for 24 weeks following a month's placebo run-in period. Doses were doubled after 12 weeks of treatment. - Amiloride 10-20 mg (n=132) - Amiloride 5-10 mg + hydrochlorothiazide 12.5-25 mg (n=133) - Hydrochlorothiazide 25 mg (n=134)	Inclusion - Adults with AOBP SBP ≥140 mm Hg and HBPM SBP ≥130 mm Hg - Indication for diuretic treatment - ≥1 component of metabolic syndrome in addition to HTN Exclusion - eGFR <45 mL/min/1.73 m² - Diagnosed diabetes - Plasma potassium concentrations outside of normal ranges	- Change from baseline in AOBP and HBPM SBP at weeks 12 and 24. - Change from baseline in laboratory values (e.g., serum potassium, sodium) at weeks 12 and 24. - Adverse events up to week 24.
Amlodipine				

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
TRINITY (NCT00649389)[116]	Phase III, double-blind, randomized, parallel-group trial. N=2,492	The triple combination and olmesartan/hydrochlorothiazide arms were of interest in our review. All arms were administered once daily for 12 weeks following a three-week washout period. - Amlodipine 10 mg + olmesartan 40 mg + hydrochlorothiazide 25 mg (n=627) - Olmesartan 40 mg + hydrochlorothiazide 25 mg (n=637) - Amlodipine 10 mg + hydrochlorothiazide 25 mg (n=600) - Amlodipine 10 mg + Olmesartan 40 mg (n=628)	Inclusion - Adults with mean seated BP ≥140/90 mm Hg or ≥160/90 mm Hg (off treatment) - Diagnosed with HTN, either untreated or undergoing washout of current AHT therapy Exclusion - Mean seated BP <140/90 mm Hg - Recent history of cerebrovascular or cardiovascular disease (e.g., secondary HTN, HF, uncontrolled diabetes)	- Change from baseline in AOBP SBP and DBP at week 12. - Change from baseline in 24h ABPM at week 12 or to early termination. - Proportion of those who achieve blood pressure goal at week 12.
Rakugi 2015 (NCT01299376)[117]	Phase III, double-blind, randomized, active-controlled trial, followed by a 44-week open-label extension period. N=285	All arms were administered once daily for 8 weeks following an 8-week single-blind period with losartan 50 mg and hydrochlorothiazide 12.5 mg. - Amlodipine 5 mg + losartan 50 mg + hydrochlorothiazide 12.5 mg (n=141) - Losartan 50 mg + hydrochlorothiazide 12.5 mg (n=145)	Inclusion - Japanese adults (aged 20-80 years) with HTN despite taking one or two AHTs - Mean trough sitting SBP ≥140 but <200 mm Hg, and DBP ≥90 but <110 mm Hg Exclusion - Treatment with ≥2 AHTs - Secondary HTN, malignant HTN or hypertensive encephalopathy	- Change from baseline in trough sitting SBP and DBP at week eight. - Adverse events up to week eight.

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
Higaki 2017[118]	Phase III, double-blind, randomized, active-controlled, parallel-group trial, followed by a 52-week open-label extension period. N=285	All arms were administered once daily for 8 weeks following a 6-week run-in period with telmisartan 80 mg and hydrochlorothiazide 12.5 mg. - Amlodipine 5 mg + telmisartan 80 mg + hydrochlorothiazide 12.5 mg (n=68) - Telmisartan 80 mg + hydrochlorothiazide 12.5 mg (n=64)	Inclusion - Japanese adults (aged ≥20 years) with BP not at goal after the run-in period - Taking 2-3 AHTs - Mean seated SBP ≤ 200 mm Hg and DBP ≥90 but ≤114 mm Hg Exclusion - Secondary HTN - Current or history of significant cerebrovascular or CVD (e.g., HF, MI, stroke/TIA)	- Change from baseline in trough sitting SBP and DBP at weeks four and eight. - Change from baseline in 24h ABPM in SBP and DBP at week four. - Proportion of patients with BP <140/90 mm Hg at weeks eight and 60. - Adverse events up to weeks eight and 60.
Calhoun 2009[59]	Double-blind, randomized, parallel-group, active-controlled trial. N=2,271	The triple combination and valsartan/hydrochlorothiazide arms were of interest in our review. All arms were administered for 9 weeks following a month's placebo run-in period. Doses could be increased at week three. - Amlodipine 5-10 mg + valsartan 160-320 mg + hydrochlorothiazide 12.5-25 mg (n=583) - Valsartan 160-320 mg + hydrochlorothiazide 12.5-25 mg (n=559) - Amlodipine 5-10 mg + valsartan 160-320 mg (n=568)	Inclusion - Adults with moderate-or-severe HTN (seated BP ≥145/100 mm Hg) - Discontinued AHTs after ≥1-week placebo run-in period Exclusion - Treatment with ≥4 AHTs - Seated BP ≥140/90 mm Hg despite taking 3 AHTs; seated BP ≥180/110 mm Hg despite taking two AHTs; seated BP <140/90 mm Hg, untreated - Serum potassium <3.2 mmol/L	- Between-treatment comparison of change from baseline in AOBP SBP and DBP at week nine. - Adverse events up to week nine.

Trial Name (NCT)	Study Design	Arms and Dosing Regimen	Key Inclusion/Exclusion Criteria	Key Outcomes
		- Amlodipine 5-10 mg + hydrochlorothiazide 12.5-25 mg (n=561)	- Serum sodium <132 mmol/L - History of cerebrovascular or cardiovascular disease (e.g., TIA, MI, type 1 diabetes, uncontrolled type 2 diabetes HF)	

ABPM: Ambulatory Blood Pressure Monitoring, ACEi: angiotensin-converting enzyme inhibitor, ACS: acute coronary syndrome, AHTs: antihypertensives, AOBP: automated in-office blood pressure, ARB: angiotensin II receptor blocker, BAX: baxdrostat, BID: twice daily, BMI: body mass index, BP: blood pressure, CCB: calcium channel blocker, CKD: chronic kidney disease, CVD: cardiovascular disease, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, ESKD: End-Stage Kidney Disease, HbA1c: hemoglobin A1c, HBPM: home blood pressure monitoring, HF: heart failure, HTN: hypertension, kg/m^2: kilogram per square meter, LOR: lorundrostat, mcg/dL: micrograms per deciliter, mEq/L: milliequivalents per liter, mg: milligrams, MI: myocardial infarction, mm Hg: millimeters of mercury, mmol/L: millimoles per liter, mL/min/1.73m²: milliliters per minute per 1.73 square meters, MRAs: mineralocorticoid receptor antagonists, n: number, NHYA: New York Heart Association, OSA: obstructive sleep apnea, QD: once daily, RAAS: renin-angiotensin-aldosterone system, rHTN: resistant hypertension, SBP: systolic blood pressure, SDHDS: South Danish Hypertension and Diabetes Study, TIA: transient ischemic attack, UACR: urine albumin-to-creatinine ratio, 24h: 24-hour

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Title, NCT, and Trial Sponsor	Study Design	Arms	Inclusion Criteria and Patient Population	Primary Outcomes	Estimated Completion Date
BaxDuo-Arctic NCT06268873 AstraZeneca	A Phase III, double-blind, randomized study to assess the efficacy and safety of baxdrostat in combination with dapagliflozin on CKD progression in patients with CKD and high blood pressure. N=2554	- BAX + dapagliflozin - Dapagliflozin + placebo	- Adults with CKD and HTN, taking an ACEi/ARB - SBP >130 mm Hg - eGFR ≥30 to <90 mL/min/1.73 m2 - Potassium 3-4.8 mmol/L if eGFR ≥45 mL/min/1.73 m²; 3-4.5 mmol/L if eGFR <45 mL/min/1.73 m² - UACR > 200 mg/g to <5000 mg/g	Change from baseline in eGFR to post treatment (two years + 12 weeks).	February 2028
BaxDuo-Pacific NCT06742723 AstraZeneca	A Phase III, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of baxdrostat in combination with dapagliflozin on kidney outcomes and cardiovascular mortality in patients with CKD and high blood pressure. N=5000	- BAX + dapagliflozin - Dapagliflozin + placebo	- Adults with CKD and HTN, taking an ACEi/ARB - SBP >130 mm Hg - Potassium 3-4.8 mmol/L if eGFR ≥45 mL/min/1.73 m²; 3-4.5 mmol/L if eGFR <45 mL/min/1.73 m² - either (a) or (b) (a) eGFR 30-59 mL/min/1.73 m² with UACR ≥30 to ≤5000 mg/g, or UPCR ≥70 to ≤7000 mg/g (b) eGFR 60-75 mL/min/1.73 m2² with UACR ≥500 to ≤ 5000 mg/g or UPCR ≥70 to ≤ 7000 mg/g	Time to first occurrence of kidney disease progression and CV events up to 37 months.	December 2029
Prevent-HF NCT06677060 AstraZeneca	A Phase III, double-blind, randomized, placebo-controlled, event-driven	- BAX + dapagliflozin - Dapagliflozin + placebo	- Participants aged ≥40 years with established CV disease - Diagnosed with type 2 diabetes and requiring treatment	Time to first occurrence (up to 38 months) of any of the components of the composite	December 2029

Title, NCT, and Trial Sponsor	Study Design	Arms	Inclusion Criteria and Patient Population	Primary Outcomes	Estimated Completion Date
	study to assess the effect of baxdrostat in combination with dapagliflozin on risk of incident heart failure and cardiovascular death. N=11300		- History of HTN (SBP ≥130 mm Hg) - Has ≥1 additional risk factor for HF (age ≥70 years, UACR >20 mg/g, eGFR <60 mL/min/1.73 m²)	of: hospitalization for HF, HF without hospitalization, or CV death	
Transform-HTN NCT05968430 Mineralys	An OLE to assess the long-term efficacy and safety of lorundrostat in patients with hypertension. N=1076	Open-label: - LOR QD for 52 weeks RTW substudy of Launch-HTN, starting at week 12: - LOR QD for four weeks - Placebo QD for four weeks Optional continuation period: - LOR QD for 52 weeks	Adults who completed a lorundrostat study with the option of transitioning to the OLE study. A Randomized Treatment Withdrawal (RTW) substudy will be performed in a subset of patients from Launch-HTN. Patients who complete the open label treatment period could continue until marketing authorization or early termination of the trial.	Change from Launch-HTN baseline AOBP SBP at week 36 in patients who only received LOR in Launch-HTN and Transform-HTN. Change from RTW AOBP SBP baseline (week 12) at week 16 (RTW week four).	December 2026

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)
ACEi: angiotensin-converting enzyme inhibitor, AHT: antihypertensives, ARB: angiotensin receptor blocker, BAX: baxdrostat, BMI: body mass index, BP: blood pressure, CKD: chronic kidney disease, CV: cardiovascular, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, HF: heart failure, LOR: lorundrostat, mg: milligrams, mg/g: milligram per gram, mm Hg: millimeters of mercury, mmol/L: millimoles per liter, mL/min/1.73m²: milliliters per minute per 1.73 square meters, n: number, OLE: open-label extension, QD: once daily, RTW: randomized treatment withdrawal, SBP: systolic blood pressure, UACR: urine albumin-to-creatinine ratio, UPCR: urine protein-to-creatinine ratio

D5. Previous Systematic Reviews and Technology Assessments

Tian et al. 2024: Efficacy of pharmacological and interventional treatment for resistant hypertension: a network meta-analysis[120]

A systematic review and frequentist NMA of 24 RCTs (3,458 patients) evaluated 12 treatments for resistant hypertension: spironolactone, doxazosin, β-blocker, clonidine, darusentan, guanfacine, various types of kidney sympathetic denervation, lifestyle intervention, continuous positive airway pressure, and baroreflex activation therapy. Spironolactone ranked best, reducing office SBP by -13.30 mm Hg (95% CI: -17.89 to −8.72) and 24-hour SBP by -8.46 mm Hg (95% CI: -12.54 to -4.38) (both p<0.0001). An exploratory analysis incorporating data from the then-recently published BaxHTN Phase II trial for baxdrostat showed comparable office SBP reductions between spironolactone (-11.17 mm Hg [95% CI: -14.37 to -7.97]; p <0.0001) and baxdrostat (-11.00 mm Hg [95% CI: -17.38 to -4.62]; p=0.0007).

Dewi 2025: Comparative efficacy and safety of aldosterone synthase inhibitors in hypertension: a Bayesian network meta-analysis of randomized controlled trials[121]

A Bayesian NMA of six RCTs (2,149 patients) evaluated baxdrostat, osilodrostat, and lorundrostat in hypertensive adults: Compared with placebo, baxdrostat 2 mg once daily significantly reduced SBP by -11.0 mm Hg and ranked highest for SBP lowering (SUCRA 77%), while osilodrostat 1 mg once daily significantly lowered SBP (-7.6 mm Hg) and lorundrostat 50 mg once daily also significantly reduced SBP (-9.1 mm Hg). Adverse events were mostly mild, serious events were uncommon, and no drug-related deaths were reported.

Elbahloul et al. 2026: Aldosterone synthase inhibitors for resistant or uncontrolled hypertension: a network meta-analysis of randomized clinical trials[122]

A frequentist random-effects NMA of six RCTs (2,725 patients) assessed baxdrostat, lorundrostat, and osilodrostat for resistant/uncontrolled hypertension. Baxdrostat and lorundrostat both significantly reduced SBP (baxdrostat: -8.81 mm Hg, 95% CI: -10.94 to -6.67; lorundrostat: -8.42 mm Hg, 95% CI: -11.05 to -5.78). Neither drug differed from placebo in risk for serious adverse events. Both drugs increased serum potassium (baxdrostat: +0.37 mmol/L, p=0.03; lorundrostat: +0.43 mmol/L, p<0.01) and significantly raised hyperkalemia risk versus placebo (Risk Ratio: 9.14 [95% CI : 1.21 to 68.91] and 7.28 [95% CI : 1.77 to 29.86], respectively).

D6. Heterogeneity and Subgroups

Table D6.1 Subgroup Data from Pivotal Trials[20,22,23]

Drug			Lorundrostat		Baxdrostat			
Trial			Launch-HTN		BaxHTN		Bax24	
Arm			50 mg	Placebo	2 mg	Placebo	2 mg	Placebo
N			808	270	266	263	108	109
Number of AHTs	2	n	318	112	67	71	NA	
		LSMD in SBP (CI)*	*-8.8 (-13.2 to -4.6)*		-10.1 (-15.3 to -4.9)			
	≥3	n	490	158	199	192		
		LSMD in SBP (CI)*	*-9.1 (-13.4 to -4.7)*		-9.8 (-13.1 to -6.4)			
Age, Years	<65	n	471	161	145	138	60	61
		LSMD in SBP (CI)*	*-9.3 (-13.2 to -5.4)*		-11.4 (-15.5 to -7.4)		-15.3 (-19.1 to -11.6)	
	≥65 to <75	n	265	80	88	91	20	23
		LSMD in SBP (CI)*	*-7 (-11.4 to -2.4)*		-7.9 (-12.6 to -3.2)		-9.8 (-17.4 to -2.3)	
	≥75	n	72	29	33	34	9	11
		LSMD in SBP (CI)*	*-11.6 (-17.4 to -5.9)*		-7.7 (-14 to -1.4)		NA	
Sex	Female	n	374	132	103	102	29	34
		LSMD in SBP (CI)*	*-9.5 (-13.5 to -5.4)*		-11.6 (-16.4 to -6.7)		-14.8 (-20.6 to -8.9)	
	Male	n	434	138	163	161	60	61
		LSMD in SBP (CI)*	*-8.8 (-12.6 to -5.2)*		-9 (-12.4 to -5.6)		-13.6 (-17.4 to -9.8)	
Race/ Ethnicity	Black/ African American	n	223	87	21	15	4	5
		LSMD in SBP (CI)*	*-6.8 (-11.6 to -2)*		-9.5 (-21.1 to 2.1)		NA	
	Asian	n	NR		72	72	14	13
		LSMD in SBP (CI)*			-8.9 (-14.1 to -3.6)		-16.1 (-26.1 to -6)	
	White	n	554	175	168	166	70	77
		LSMD in SBP (CI)*	*-9.1 (-12.9 to -5.5)*		-9.6 (-13.1 to -6.2)		-13.7 (-17.2 to -10.2)	
	Hispanic /Latino	n	NR		39	38	21	19
		LSMD in SBP (CI)*			-12.7 (-19.8 to -5.6)		-12 (-19.6 to -4.5)	
Baseline SBP, mm Hg	<140	n	218	73	NR		46	49
		LSMD in SBP (CI)*	*-7.2 (-11.6 to -2.8)*				-13.7 (-18 to -9.4)	
	<145	n	NR		92	92	NR	
		LSMD in SBP (CI)*			-8.3 (-13.3 to -3.3)			
	140-59	n	445	144	NR		NR	
		LSMD in SBP (CI)*	*-11.2 (-15.2 to -7.2)*					
	≥140	n	NR		NR		43	46
		LSMD in SBP (CI)*					-15.4 (-20.2 to -10.7)	
	≥145	n	NR		174	171	NR	
		LSMD in SBP (CI)*			-10.7 (-14.1 to -7.3)			
	≥160	n	145	53	NR		NR	
		LSMD in SBP (CI)*	*-8 (-12.7 to -3.3)*					
eGFR, mL/min/ 1.73 m^2	<60	n	173	49	30	29	7	12
		LSMD in SBP (CI)*	*-9.3 (-14.2 to -4.6)*		-8.4 (-17.6 to 0.8)		NA	
	60-89	n	401	150	NR		NR	
		LSMD in SBP (CI)*	*-9.6 (-13.4 to -5.5)*					
	≥60	n	NR		236	234	82	83
		LSMD in SBP (CI)*			-10.1 (-13 to -7.1)		-13.5 (-16.9 to -10.1)	
	≥90	n	234	71	NR		NR	

Drug			Lorundrostat		Baxdrostat			
Trial			Launch-HTN		BaxHTN		Bax24	
Arm			50 mg	Placebo	2 mg	Placebo	2 mg	Placebo
N			808	270	266	263	108	109
eGFR, mL/min/ 1.73 m^2	**≥90**	**LSMD in SBP (CI)***	*-8 (-12.6 to -3.4)*		NR		NR	

AHTs: antihypertensives, eGFR: estimated glomerular filtration rate, CI: confidence interval, HTN: hypertension, LSMD: least-squares mean difference, mg: milligrams, mL/min/1.73 m^2: milliliters per minute per 1.73 square meters, mm Hg: millimeters of mercury, n: number, NA: not applicable, NR: not reported, SBP: systolic blood pressure

*SBP was measured as in-office for Launch-HTN and BaxHTN, and as ambulatory for Bax24. Confidence intervals were reported as 90% for Launch-HTN, and 95% for BaxHTN and Bax24.

Note: italics indicate data was digitized. Treatment effect was not analyzed for subgroups with fewer than 10 participants within treatment groups for Bax24.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[123]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[124]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

We modeled two populations consisting of patients with 1) resistant hypertension with blood pressure above goal and not on spironolactone, eplerenone, or amiloride (Population 1) and 2) uncontrolled hypertension despite the use of two antihypertensive agents who do not tolerate a third first-line agent recommended by clinical guidelines (Population 2). Baseline characteristics were informed by the BAX24, BaxHTN, and LAUNCH-HTN clinical trials.[20,22,23] BAX24 enrolled only resistant hypertension patients, whereas BaxHTN and LAUNCH-HTN enrolled both resistant and uncontrolled hypertension patients. Because BaxHTN and LAUNCH-HTN did not report characteristics for their resistant and uncontrolled hypertension patients separately, and the patient populations are fairly similar across all three trials, we applied a weighted average of their baseline characteristics to define our modeled population. For each intervention we modeled the dose most likely to be used in clinical practice, namely the 50 mg dose for lorundrostat and the 2 mg dose for baxdrostat, both administered as once daily tablets.

Table E1.2. Base-Case Model Cohort Characteristics

	BAX24 (n=217)	BaxHTN (n=530)	LAUNCH-HTN (n=813)	Weighted Average
Mean Age	60.50	61.85	61.73	61.60
Percent Male	64.50	61.32	53.26	57.56
SBP, Mean	147.60	149.05	148.93	148.79
DBP, Mean	85.55	85.80	87.57	86.69
eGFR, Mean	85.55	84.20	90.47	87.66
Type 2 Diabetes (%)	34.10	41.51	32.23	35.64
BMI	32.00	31.15	32.87	32.16

BMI: body mass index, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Baxdrostat (BAXFENDY)
- Lorundrostat

The comparators for these interventions were:

- Spironolactone
- Eplerenone
- Amiloride

E2. Model Inputs and Assumptions

Model Inputs

Clinical Inputs

The model translated each treatment's effect on SBP into cardiovascular and kidney event risk. Three sets of clinical inputs drove this. First, the baseline probabilities of transitioning from the hypertension alone state to each event state were derived from published multivariate risk equations applied to the modeled cohort. Second, the SBP reduction achieved by each intervention and comparator was based on ICER's internal network meta-analyses. Third, the relative effect of SBP lowering on each event type was informed by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC).[9] The risk equations used patients' baseline SBP to estimate untreated, control-arm event risk, while the incremental SBP reduction achieved by each treatment was

applied separately through the BPLTTC effect estimates. Each input was identified by literature with estimates to the US resistant and uncontrolled hypertension population preferred where data permitted. If suitable direct evidence existed linking a treatment's impact on cardiovascular and kidney events, we calibrated the event risk estimates to these targets.

Transition Probabilities

Baseline probabilities of transitioning from the hypertension alone state to the cardiovascular and kidney event states were derived from published multivariate risk equations, consistent with prior economic evaluations of hypertension treatment.[62,63] Risk of stroke, coronary heart disease, and heart failure were estimated using Framingham Heart Study risk equations, risk of myocardial infarction using the PROCAM risk equation, and risk of end-stage kidney disease.[125-130] Each equation was applied to the modeled cohort's baseline characteristics (including age, sex, baseline SBP, diabetes status, and lipid profile) to set control-arm event risks, with variables not informed by the clinical trials for lorundrostat and baxdrostat obtained from the literature (Table E2.1). For patients in the post-MI or ESKD health state, these baseline transition probabilities were adjusted upward by elevated-risk hazard ratios to capture their higher likelihood of a subsequent event, namely 1.44 for patients post-myocardial infarction and 3.4 for those with end-stage kidney disease.[66,67] This adjustment was applied uniformly regardless of the number of prior events a patient had experienced.

Table E2.1. Inputs for Risk Equations

Input	Value	Source
Proportion in Menopause, %	95.00%	de Kat et al. 2017[131]
Triglycerides (mg/dL)	191.6	Lee et al. 2016[132]
HDL (mg/dL)	44.9	Lee et al. 2016[132]
LDL (mg/dL)	103.1	Lee et al. 2016[132]
Gamma-glutamyl Transferase (U/L)	25.5	Abbassi et al. 2012[133]
Total Cholesterol (mg/dL)	182.5	Lee et al. 2016[132]
Proportion of Smokers, %	25.4%	Lee et al. 2016[132]
Proportion of Alcohol Drinkers, %	66.3%	NCHS Data Brief 2020[134]
Proportion with CV Family History, %	12.6%	Moonesinghe et al. 2019[135]
Proportion with LVH, %	8.7%	Lee et al. 2016[132]
Proportion with AF, %	15.5%	Bhatt et al. 2016 [136]
Male Vital Capacity, (L)	4.02	Enright et al. 1995[137]
Female Vital Capacity, (L)	2.57	Enright et al. 1995[137]
Proportion with Valvular Disease, %	2.5%	Nkomo et al. 2006[138]
Proportion with Cardiomegaly, %	11.8%	Sigurdsson et al. 1996[139]
Heart Rate (beats per minute)	68	Vaclavik et al. 2014[140]

CV: cardiovascular, HDL: high-density lipoprotein, L: Liter, LDL: low-density lipoprotein, LVH: left ventricular hypertrophy, mg/dL: milligrams per deciliter, U/L: units per liter

Each intervention's clinical benefit was modeled through its effect on SBP. For each treatment and comparator, we used SBP reduction estimates from ICER's internal network meta-analyses and

translated these into a change in event risk using outcome-specific effect estimates from the BPLTTC, an individual participant-level data meta-analysis of 48 large randomized trials in more than 340,000 patients.[9] The BPLTTC reported hazard ratios (HR) and relative risks (RR) per 5 or 10 mm Hg SBP reduction for cardiovascular and kidney events.[9,73] The BPLTTC found treatment effects to be proportional to the magnitude of SBP reduction achieved, with no evidence of effect modification by baseline SBP or prior CV disease. The event-specific multiplier was applied to the baseline transition probability derived from the aforementioned risk equations, resulting in a treatment-adjusted transition probability for each cycle. The BPLTTC reported a single combined ischemic heart disease outcome encompassing both MI and other ischemic heart disease. We therefore applied this hazard ratio (0.92 per 5 mm Hg reduction) to both the MI and CHD disease transitions. If suitable direct evidence existed linking a treatment's impact on cardiovascular and kidney events, we calibrated the event risk estimates to these targets.

Treatment Discontinuation

Treatment discontinuation in the model reflected both the expected duration of treatment and discontinuation related to adverse events, drawn from the pivotal trials (BaxHTN for baxdrostat, Launch-HTN for lorundrostat). Across the two Phase III trials, the baxdrostat 2 mg arm had an all-cause discontinuation rate of 45 of 374 patients, equivalent to a 13% 3-month probability, and the lorundrostat 50 mg arm had a rate of 50 of 541 patients, equivalent to a 10% 3-month probability.[20,22,23] These trial-based three-month probabilities were applied only to the first cycle for lorundrostat and baxdrostat, approximating the follow-up length of the pivotal trials. After the first cycle, we applied a declining persistence function to both interventions, drawn from a study of treatment persistence in patients with hypertension.[141] We used the calcium channel blocker group from that study, as its persistence was the median across the drug classes evaluated, and we applied the same function to the comparator groups (spironolactone, eplerenone, and amiloride) from the first cycle onward. For spironolactone, we applied a hazard ratio of approximately 1.45 throughout to reflect its higher risk of discontinuation relative to eplerenone given the worse tolerability of spironolactone due to side effects. This was based on a meta-analysis of patients with heart failure.[142] No head-to-head estimate in a hypertension population was identified. In a scenario analysis, we evaluated full persistence, in which no patients discontinued treatment. As described in Section 2.2, patients who discontinued an intervention were modeled as returning to their baseline antihypertensive regimen, at which point their SBP returned to baseline and the associated treatment effect ended.

Adverse Events

For each intervention, the incidence of treatment-related serious adverse events is low (<5%), and prior cost-effectiveness models of hypertension treatment omit adverse events entirely.[63-65] Consistent with this precedent, we did not include intervention-related disutilities or costs related to adverse events in the model. While the aldosterone synthase inhibitors are associated with

hyperkalemia and hyponatremia, these events were infrequent in the baxdrostat and lorundrostat trials and were not expected to materially affect costs or quality of life over the model horizon. Although clinical experts noted that gynecomastia can be a problem with spironolactone, prior models that included spironolactone did not model gynecomastia as an explicit adverse event, but instead assumed it acts through discontinuation.[143-146] We captured this here by applying an elevated discontinuation rate for spironolactone, which reflects its higher risk of treatment withdrawal (including withdrawal related to gynecomastia) relative to the other drugs under consideration in the model, as described in the Discontinuation section above.

Economic Inputs

Table E2.2. Dose, Frequency of Administration, and Annual Monitoring and Administration Utilization

Generic Name	Lorundrostat	Baxdrostat	Spironolactone	Eplerenone	Amiloride	Amlodipine
Brand Name	Not available	BAXFENDY™	Aldactone®	Inspra®	Midamor®	Norvasc®
Manufacturer	Mineralys Therapeutics	AstraZeneca	Generic	Generic	Generic	Generic
Route of Administration	oral	oral	oral	oral	oral	oral
Dosing	50 mg once daily	1 or 2 mg once daily	25-100 mg once daily	50 mg once to twice daily	5-10 mg once daily	5-10 mg once daily

mg: milligram

Health Care Utilization Costs

Non-drug health care costs were applied as health state costs reflecting the direct medical care associated with each health state in the model. Background costs of managing hypertension alone were applied to patients in the hypertension alone state, and condition-specific costs were applied to patients in each cardiovascular and kidney event state (stroke, myocardial infarction, other coronary heart disease, heart failure, and end-stage kidney disease). For patients in combined health states, costs were applied additively across the contributing conditions, consistent with prior cost-effectiveness models of hypertension.[64] For acute cardiovascular events, a first-cycle cost reflecting acute hospitalization and care was applied in the cycle of the event, followed by ongoing annual costs for the post-event state in subsequent cycles.

Table E2.3. Health State Costs

Health State	Annual Cost*	Source
Hypertension (Annual)	$3,211	Wang et al. 2024[3]
Stroke (Acute and Annual)	$20,442 / $20,697	Johnson et al. 2016[147] / [148,149]
MI (Acute and Annual)	$25,832 / $17,106	Cowper et al. 2019[150] / Kazi et al. 2024[148], Kazi et al 2016[151]
Coronary Heart Disease (Annual)	$13,798	Kazi et al. 2024[148]
HF (Index Hospitalization and Annual)	$16,671 / $33,890	Urbich et al. 2020[152]
ESKD (Annual)	$108,953	USRDS Annual Report 2025[80]

ESKD: end-stage kidney disease, HF: heart failure, MI: myocardial infarction

*Adjusted to 2025 United States Dollar

Productivity Costs

Productivity costs were estimated for the patient using literature-based estimates of annual productivity loss calculated from the ratio of direct versus indirect burden of each chronic condition management.[153-155]

Table E2.4. Modified Societal Perspective Health State Costs

Health State	Annual Cost*	Source
Stroke (Annual)	$16,781	American Heart Association / American Stroke Association[153]
MI (Annual)	$19,028	American Heart Association / American Stroke Association[153]
Coronary Heart Disease (Annual)	$7,092	American Heart Association / American Stroke Association[153]
HF (Annual)	$16,004	Heidenreich 2022[154]
ESKD (Annual)	$17,650	Moyneur 2008[155]

ESKD: end-stage kidney disease, HF: heart failure, MI: myocardial infarction

*Adjusted to 2025 United States Dollar

E3. Results

Table E3.1 shows the clinical outcomes per 1,000 patients projected from our model. Differences in lifetime clinical events (MI, stroke, HF, CHD, ESKD) per 1,000 patients were small because the incremental blood-pressure benefit between therapies were modest in magnitude and limited in duration. First, the achieved SBP reductions were similar across agents (roughly 9–11 mm Hg for baxdrostat, lorundrostat, and spironolactone and 7–9 mm Hg for eplerenone and amiloride), so the SBP gap that drove differential event risk was only a few mm Hg. Second, the treatment effect on event risk applied only while patients remained on therapy, and persistence was low based on the literature. The majority of patients discontinued within the first few years and reverted to baseline risk so the time horizon where between-treatment arm differences could accrue was brief. Third, baxdrostat and lorundrostat carried higher discontinuation than the comparators after roughly two

years, which further narrowed their cumulative on-treatment advantage. As a result, the modest SBP differences translated into only small differences in lifetime events once real-world discontinuation was applied. Consistent with this mechanism, the model's "no discontinuation" scenario, in which patients remained on therapy and retained the full SBP effect, produced clearly separated clinical event counts across treatments.

Table E3.1. Base Case Results for Clinical Outcomes per 1,000 Patients by Treatment

Treatment	MI	Stroke	CHD	HF	ESKD
Baxdrostat	197	150	225	157	11
Lorundrostat	197	151	226	158	11
Spironolactone	198	152	227	159	11
Eplerenone	197	151	226	158	11
Amiloride	198	152	226	159	11

CHD: coronary heart disease, ESKD: end-stage kidney disease, HF: heart failure, MI: myocardial infarction

E4. Sensitivity Analyses

To assess the effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes for baxdrostat versus spironolactone, eplerenone, and amiloride as well as for lorundrostat versus the same comparators. Although the incremental cost-effectiveness ratio is the outcome typically reported in a one-way sensitivity analysis, it is unstable when the incremental effectiveness is close to zero, as was the case in many of the pairwise comparisons. In these cases, both the low and high values of a given input move the results to the same side of the base-case estimate. This made the direction and magnitude of each parameter's effect difficult to interpret. We therefore reported incremental total costs and incremental evLYs gained as separate outcomes, which provided a more interpretable visualization of how each parameter influenced the results. All tornado diagrams are shown in Figures E4.1 through E4.12, with associated results shown in Tables E4.1 through E4.12.

In the assessment of baxdrostat versus the comparator antihypertensive drugs, the SBP reduction for baxdrostat and the comparator drug versus placebo were the largest drivers, followed by the cost of baxdrostat, discontinuation assumptions, and treatment effect assumptions, in varying order (Figures and Tables E4.1 – E4.6). None of the lower and upper inputs changed the cost-effectiveness conclusion as all results remained above commonly accepted thresholds. In some cases, such as baxdrostat versus eplerenone, the lowest effectiveness assumption for baxdrostat (its lowest input for SBP reduction) or the highest effectiveness assumption for eplerenone (its highest input for SBP reduction) led to baxdrostat being dominated by eplerenone.

In the assessment of lorundrostat versus the comparator antihypertensive drugs, similar parameters were most influential in the model and similar impacts were seen where the lowest

effectiveness assumption for lorundrostat or the highest effectiveness assumption for the comparator led to lorundrostat being dominated.

Figure E4.1. Tornado Diagram for Baxdrostat versus Spironolactone (Incremental evLY Gained)

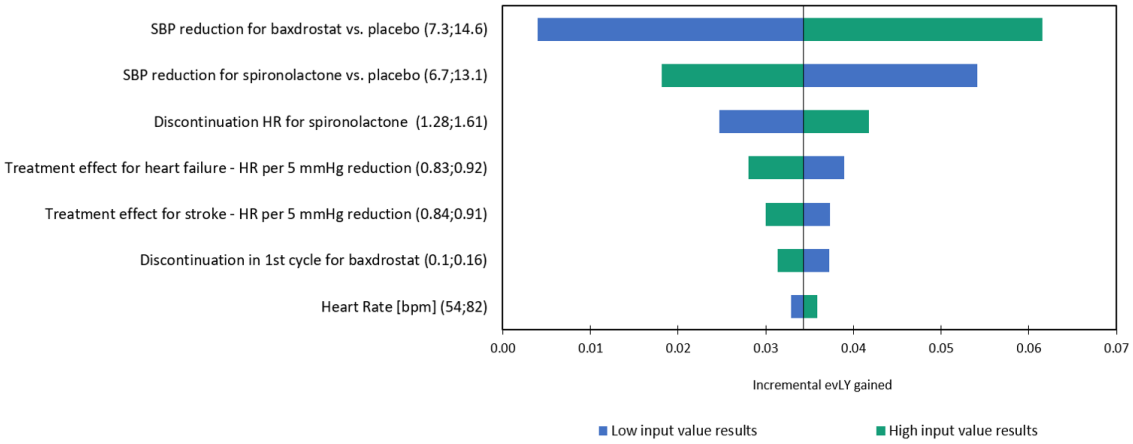


Table E4.1. Tornado Diagram Inputs and Results for Baxdrostat versus Spironolactone (Incremental per evLY Gained)

	Lower Incremental evLY gained	Upper Incremental evLY gained	Lower Input*	Upper Input*
SBP Reduction for Baxdrostat vs. Placebo	0.004	0.062	7.3	14.6
SBP Reduction for Spironolactone vs. Placebo	0.054	0.018	6.7	13.1
Discontinuation HR for Spironolactone	0.025	0.042	1.28	1.61
Treatment Effect for Heart Failure - HR per 5 mm Hg Reduction	0.039	0.028	0.83	0.92
Treatment Effect for Stroke - HR per 5 mm Hg Reduction	0.037	0.030	0.84	0.91
Discontinuation in 1st Cycle for Baxdrostat	0.037	0.031	0.10	0.16
Heart Rate (beats per minute)	0.033	0.036	54.4	81.6

evLY: equal value life year, HR: hazard ratio, mm Hg: millimeters of mercury, SBP: systolic blood pressure
*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.2. Tornado Diagram for Baxdrostat versus Spironolactone (Incremental Total Costs)

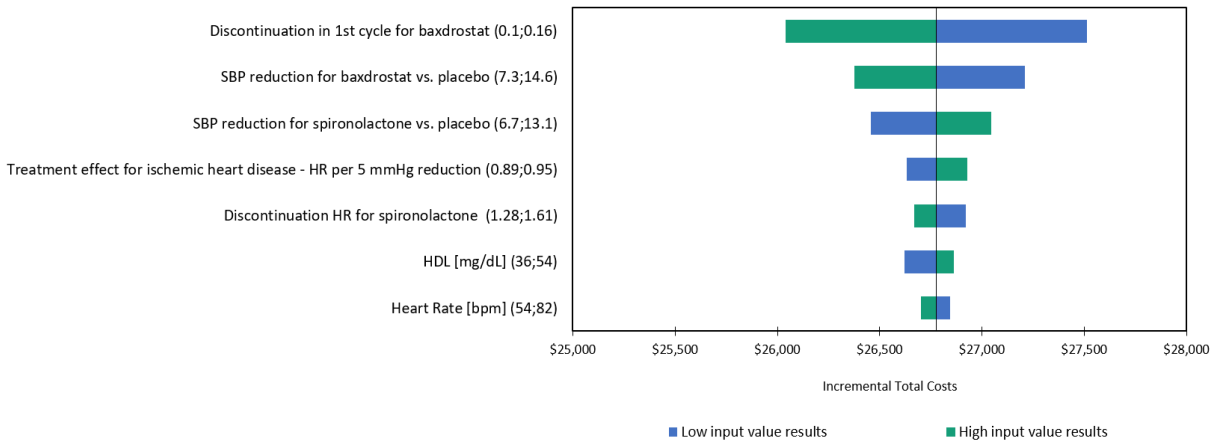


Table E4.2. Tornado Diagram Inputs and Results for Baxdrostat versus Spironolactone (Incremental Total Costs)

	Lower Incremental Total Costs	Upper Incremental Total Costs	Lower Input*	Upper Input*
Discontinuation in 1st Cycle for Baxdrostat	$26,000	$27,500	0.10	0.16
SBP Reduction for Baxdrostat vs. Placebo	$26,400	$27,200	7.3	14.6
SBP Reduction for Spironolactone vs. Placebo	$26,500	$27,000	6.7	13.1
Treatment Effect for Ischemic Heart Disease - HR per 5 mm Hg Reduction	$26,600	$26,900	0.89	0.95
Discontinuation HR for Spironolactone	$26,900	$26,700	1.28	1.61
HDL (mg/dL)	$26,600	$26,900	35.92	53.88
Heart Rate (beats per minute)	$26,700	$26,800	54.4	81.6

CE: cost-effectiveness, dL: deciliter, HDL: high-density lipoprotein, HR: hazard ratio, mg: milligrams, mm Hg: millimeters of mercury, SBP: systolic blood pressure

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.3. Tornado Diagram for Baxdrostat versus Eplerenone (Incremental evLY Gained)

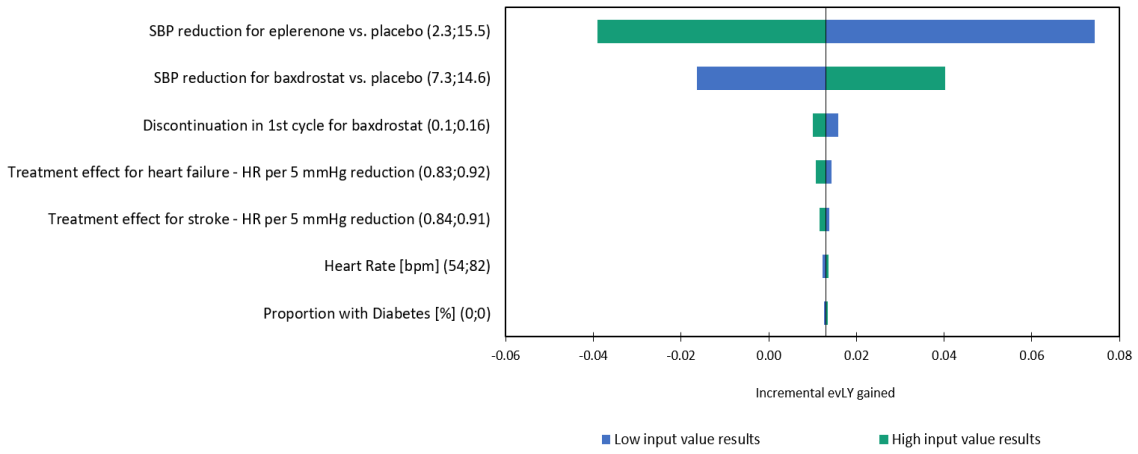


Table E4.3. Tornado Diagram Inputs and Results for Baxdrostat versus Eplerenone (Incremental per evLY Gained)

	Lower Incremental evLY gained	Upper Incremental evLY gained	Lower Input*	Upper Input*
SBP Reduction for Eplerenone vs. Placebo	-0.039	0.074	2.3	15.5
SBP Reduction for Baxdrostat vs. Placebo	-0.016	0.040	7.3	14.6
Discontinuation in 1st Cycle for Baxdrostat	0.010	0.016	0.10	0.16
Treatment Effect for Heart Failure - HR per 5 mm Hg Reduction	0.011	0.014	0.83	0.92
Treatment Effect for Stroke - HR per 5 mm Hg Reduction	0.012	0.014	0.84	0.91
Heart Rate (beats per minute)	0.012	0.014	54.4	81.6
Proportion with Diabetes (%)	0.013	0.013	0.29	0.43

evLY: equal value life year, HR: hazard ratio, mm Hg: millimeters of mercury, SBP: systolic blood pressure
*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.4. Tornado Diagram for Baxdrostat versus Eplerenone (Incremental Total Costs)

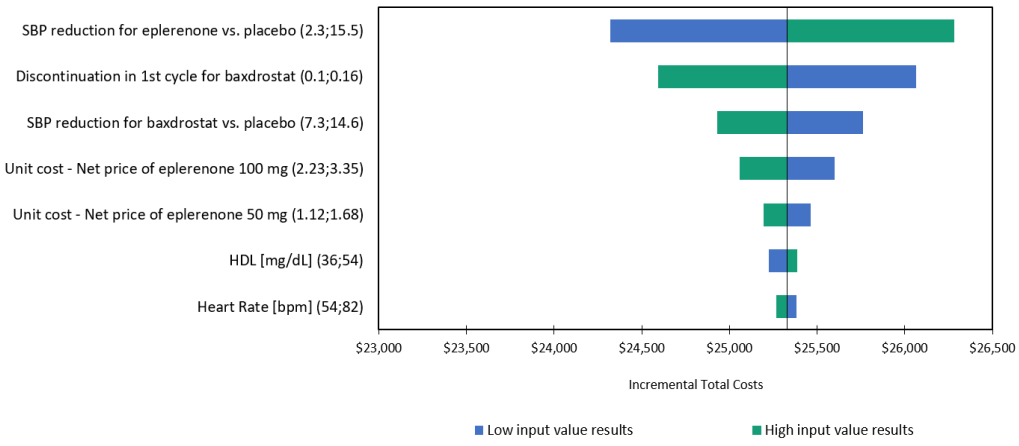


Table E4.4. Tornado Diagram Inputs and Results for Baxdrostat versus Eplerenone (Incremental Total Costs)

	Lower Incremental Total Costs	Upper Incremental Total Costs	Lower Input*	Upper Input*
SBP Reduction for Eplerenone vs. Placebo	$24,300	$26,300	2.3	15.5
Discontinuation in 1st Cycle for Baxdrostat	$24,600	$26,100	0.10	0.16
SBP Reduction for Baxdrostat vs. Placebo	$24,900	$25,800	7.3	14.6
Unit Cost - Net Price of Eplerenone 100 mg	$25,100	$25,600	2.23	3.35
Unit Cost - Net Price of Eplerenone 50 mg	$25,200	$25,500	1.12	1.68
HDL (mg/dL)	$25,200	$25,400	35.92	53.88
Heart Rate (beats per minute)	$25,300	$25,400	54.4	81.6

CE: cost-effectiveness, dL: deciliter, HDL: high-density lipoprotein, HR: hazard ratio, mg: milligrams, mm Hg: millimeters of mercury, SBP: systolic blood pressure

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.5. Tornado Diagram for Baxdrostat versus Amiloride (Incremental evLY Gained)

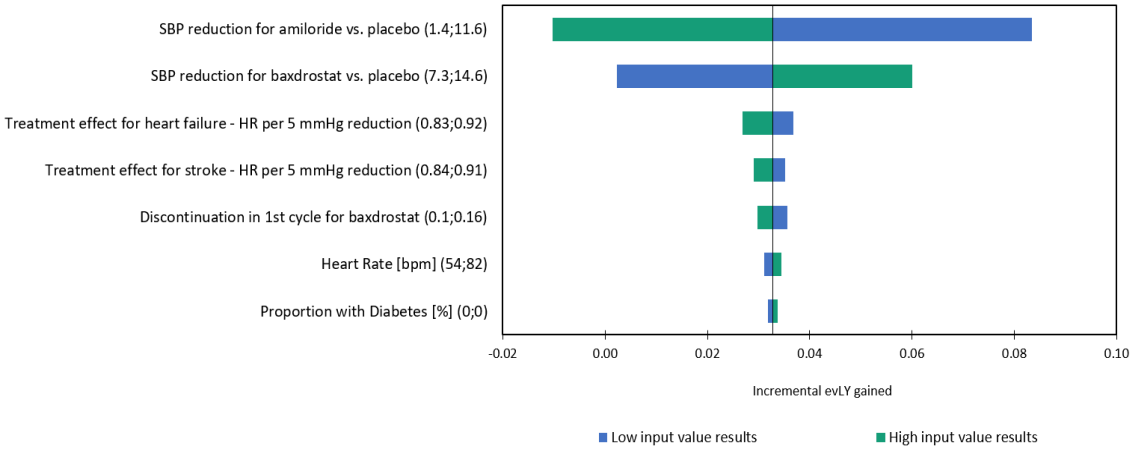


Table E4.5. Tornado Diagram Inputs and Results for Baxdrostat versus Amiloride (Incremental per evLY Gained)

	Lower Incremental evLY gained	Upper Incremental evLY gained	Lower Input*	Upper Input*
SBP Reduction for Amiloride vs. Placebo	-0.010	0.083	1.4	11.6
SBP Reduction for Baxdrostat vs. Placebo	0.002	0.060	7.3	14.6
Treatment Effect for Heart Failure - HR per 5 mm Hg Reduction	0.027	0.037	0.83	0.92
Treatment Effect for Stroke - HR per 5 mm Hg Reduction	0.029	0.035	0.84	0.91
Discontinuation in 1st Cycle for Baxdrostat	0.030	0.036	0.10	0.16
Heart Rate (beats per minute)	0.031	0.035	54.4	81.6
Proportion with Diabetes (%)	0.032	0.034	0.29	0.43

evLY: equal value life year, HR: hazard ratio, mm Hg: millimeters of mercury, SBP: systolic blood pressure

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.6. Tornado Diagram for Baxdrostat versus Amiloride (Incremental Total Costs)

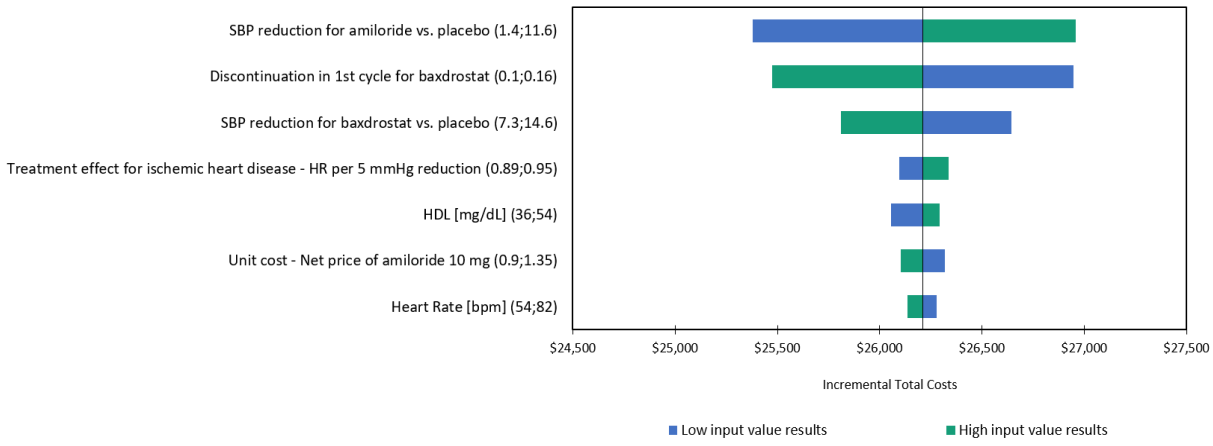


Table E4.6. Tornado Diagram Inputs and Results for Baxdrostat versus Amiloride (Incremental Total Costs)

	Lower Incremental Total Costs	Upper Incremental Total Costs	Lower Input*	Upper Input*
SBP Reduction for Amiloride vs. Placebo	$25,400	$27,000	1.4	11.6
Discontinuation in 1st Cycle for Baxdrostat	$25,500	$26,900	0.10	0.16
SBP Reduction for Baxdrostat vs. Placebo	$25,800	$26,600	7.3	14.6
Treatment Effect for Ischemic Heart Disease - HR per 5 mm Hg Reduction	$26,100	$26,300	0.89	0.95
HDL (mg/dL)	$26,100	$26,300	35.92	53.88
Unit Cost - Net Price of Amiloride 10 mg	$26,100	$26,300	0.90	1.35
Heart Rate (beats per minute)	$26,100	$26,300	54.4	81.6

CE: cost-effectiveness, dL: deciliter, HDL: high-density lipoprotein, HR: hazard ratio, mg: milligrams, mm Hg: millimeters of mercury, SBP: systolic blood pressure

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.7. Tornado Diagram for Lorundrostat versus Spironolactone (Incremental evLY Gained)

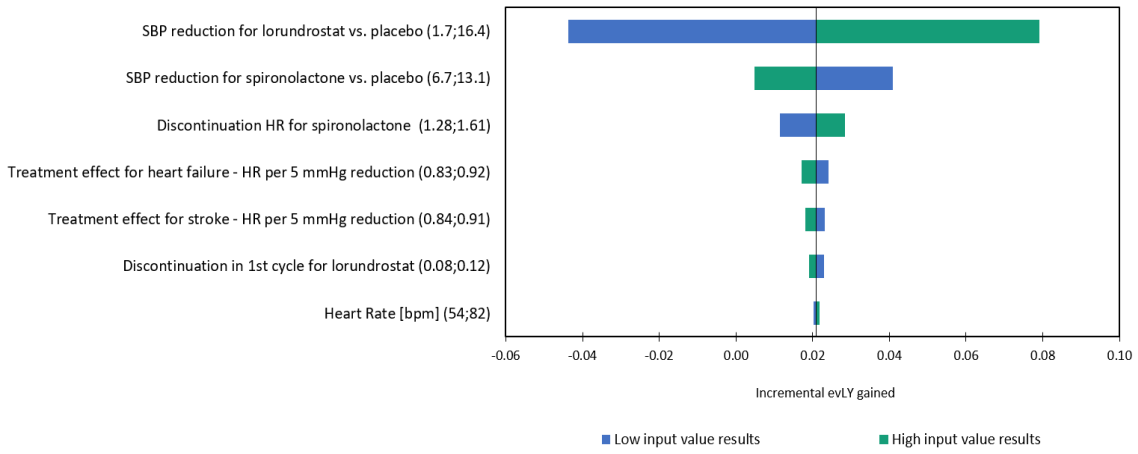


Table E4.7. Tornado Diagram Inputs and Results for Lorundrostat versus Spironolactone (Incremental per evLY Gained)

	Lower Incremental evLY gained	Upper Incremental evLY gained	Lower Input*	Upper Input*
SBP Reduction for Lorundrostat vs. Placebo	-0.044	0.079	1.7	16.4
SBP Reduction for Spironolactone vs. Placebo	0.005	0.041	6.7	13.1
Discontinuation HR for Spironolactone	0.011	0.028	1.28	1.61
Treatment Effect for Heart Failure - HR per 5 mm Hg Reduction	0.017	0.024	0.83	0.92
Treatment Effect for Stroke - HR per 5 mm Hg Reduction	0.018	0.023	0.84	0.91
Discontinuation in 1st Cycle for Lorundrostat	0.019	0.023	0.08	0.12
Heart Rate (beats per minute)	0.020	0.022	54.4	81.6

evLY: equal value life year, HR: hazard ratio, mm Hg: millimeters of mercury, SBP: systolic blood pressure
*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.8. Tornado Diagram for Lorundrostat versus Spironolactone (Incremental Total Costs)

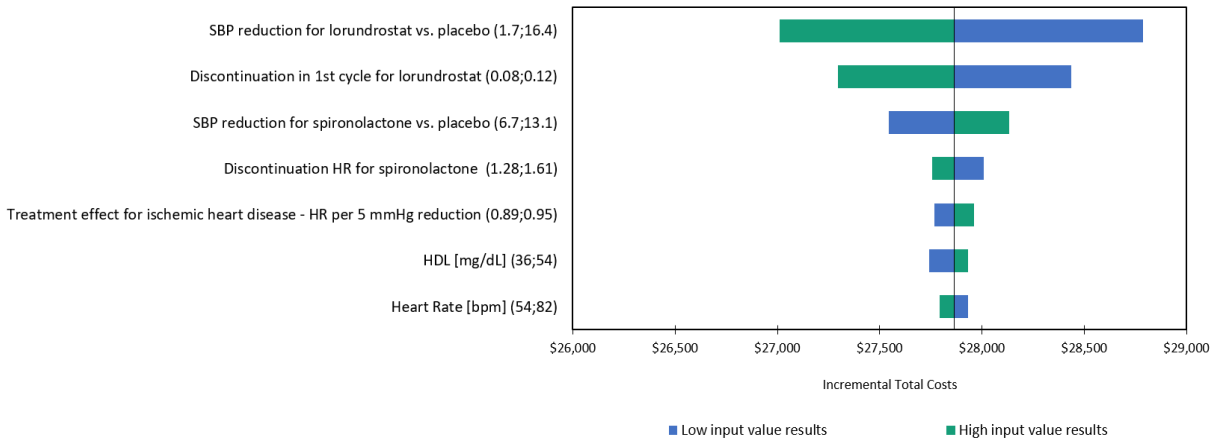


Table E4.8. Tornado Diagram Inputs and Results for Lorundrostat versus Spironolactone (Incremental Total Costs)

	Lower Incremental Total Costs	Upper Incremental Total Costs	Lower Input*	Upper Input*
SBP Reduction for Lorundrostat vs. Placebo	$27,000	$28,800	1.7	16.4
Discontinuation in 1st Cycle for Lorundrostat	$27,300	$28,400	0.08	0.12
SBP reduction for Spironolactone vs. Placebo	$27,500	$28,100	6.7	13.1
Discontinuation HR for Spironolactone	$27,800	$28,000	1.28	1.61
Treatment Effect for Ischemic Heart Disease - HR per 5 mmHg Reduction	$27,800	$28,000	0.89	0.95
HDL (mg/dL)	$27,700	$27,900	35.92	53.88
Heart Rate (beats per minute)	$27,800	$27,900	54.4	81.6

CE: cost-effectiveness, dL: deciliter, HDL: high-density lipoprotein, HR: hazard ratio, mg: milligrams, mm Hg: millimeters of mercury, SBP: systolic blood pressure

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.9. Tornado Diagram for Lorundrostat versus Eplerenone (Incremental evLY Gained)

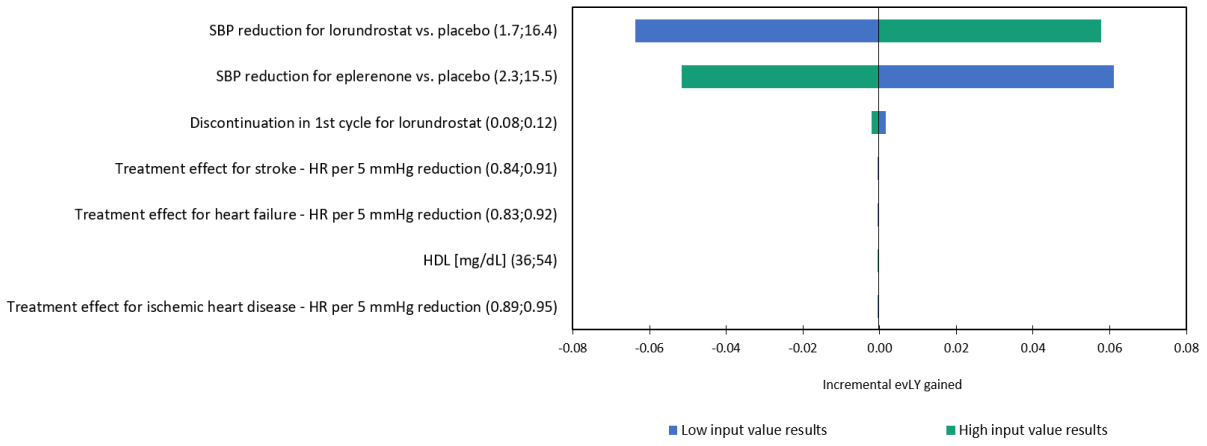


Table E4.9. Tornado Diagram Inputs and Results for Lorundrostat versus Eplerenone (Incremental per evLY Gained)

	Lower Incremental evLY gained	Upper Incremental evLY gained	Lower Input*	Upper Input*
SBP Reduction for Lorundrostat vs. Placebo	-0.064	0.058	1.7	16.4
SBP Reduction for Eplerenone vs. Placebo	-0.052	0.061	2.3	15.5
Discontinuation in 1st Cycle for Lorundrostat	-0.002	0.002	0.08	0.12
Treatment Effect for Stroke - HR per 5 mm Hg Reduction	0.000	0.000	0.84	0.91
Treatment Effect for Heart Failure - HR per 5 mm Hg Reduction	0.000	0.000	0.83	0.92
HDL (mg/dL)	0.000	0.000	35.92	53.88
Treatment Effect for Ischemic Heart Disease - HR per 5 mm Hg Reduction	0.000	0.000	0.89	0.95

evLY: equal value life year, HDL: high-density lipoprotein, HR: hazard ratio, mm Hg: millimeters of mercury, SBP: systolic blood pressure

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.10. Tornado Diagram for Lorundrostat versus Eplerenone (Incremental Total Costs)

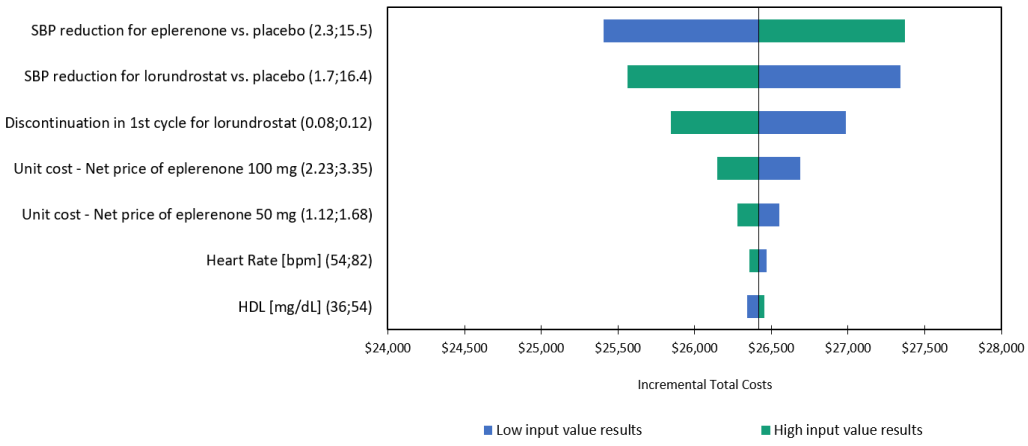


Table E4.10. Tornado Diagram Inputs and Results for Lorundrostat versus Eplerenone (Incremental Total Costs)

	Lower Incremental Total Costs	Upper Incremental Total Costs	Lower Input*	Upper Input*
SBP Reduction for Eplerenone vs. Placebo	$25,400	$27,400	2.3	15.5
SBP Reduction for Lorundrostat vs. Placebo	$25,600	$27,300	1.7	16.4
Discontinuation in 1st Cycle for Lorundrostat	$25,800	$27,000	0.08	0.12
Unit cost - Net Price of Eplerenone 100 mg	$26,100	$26,700	2.23	3.35
Unit cost - Net Price of Eplerenone 50 mg	$26,300	$26,600	1.12	1.68
Heart Rate (beats per minute)	$26,400	$26,500	54.4	81.6
HDL (mg/dL)	$26,300	$26,500	35.92	53.88

CE: cost-effectiveness, dL: deciliter, HDL: high-density lipoprotein, HR: hazard ratio, mg: milligrams, mm Hg: millimeters of mercury, SBP: systolic blood pressure

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.11. Tornado Diagram for Lorundrostat versus Amiloride (Incremental evLY Gained)

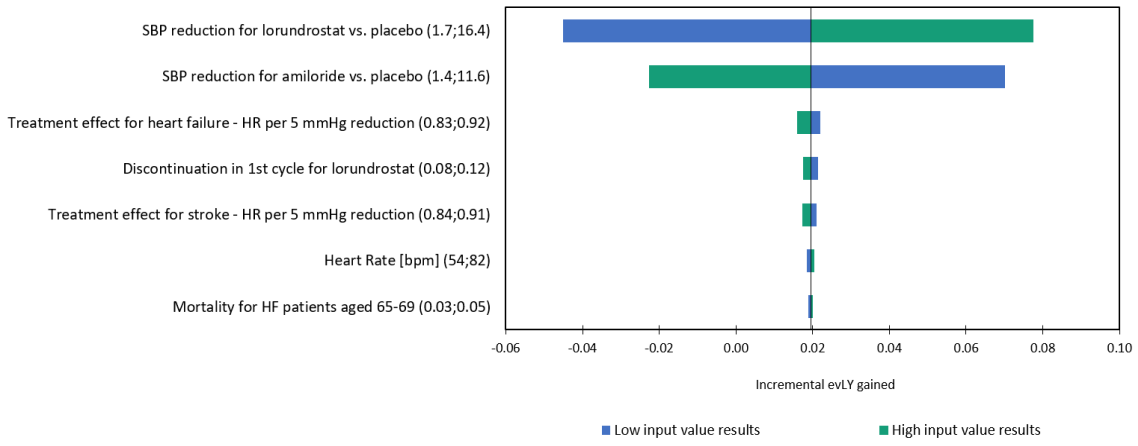


Table E4.11. Tornado Diagram Inputs and Results for Lorundrostat versus Amiloride (Incremental per evLY Gained)

	Lower Incremental evLY gained	Upper Incremental evLY gained	Lower Input*	Upper Input*
SBP Reduction for Lorundrostat vs. Placebo	-0.045	0.078	1.7	16.4
SBP Reduction for Amiloride vs. Placebo	-0.023	0.070	1.4	11.6
Treatment Effect for Heart Failure - HR per 5 mm Hg Reduction	0.016	0.022	0.83	0.92
Discontinuation in 1st Cycle for Lorundrostat	0.018	0.021	0.08	0.12
Treatment Effect for Stroke - HR per 5 mm Hg Reduction	0.017	0.021	0.84	0.91
Heart Rate (beats per minute)	0.019	0.021	54.4	81.6
Mortality for HF Patients Aged 65-69	0.019	0.020	0.03	0.05

evLY: equal value life year, HR: hazard ratio, mm Hg: millimeters of mercury, SBP: systolic blood pressure

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.12. Tornado Diagram for Lorundrostat versus Amiloride (Incremental Total Costs)

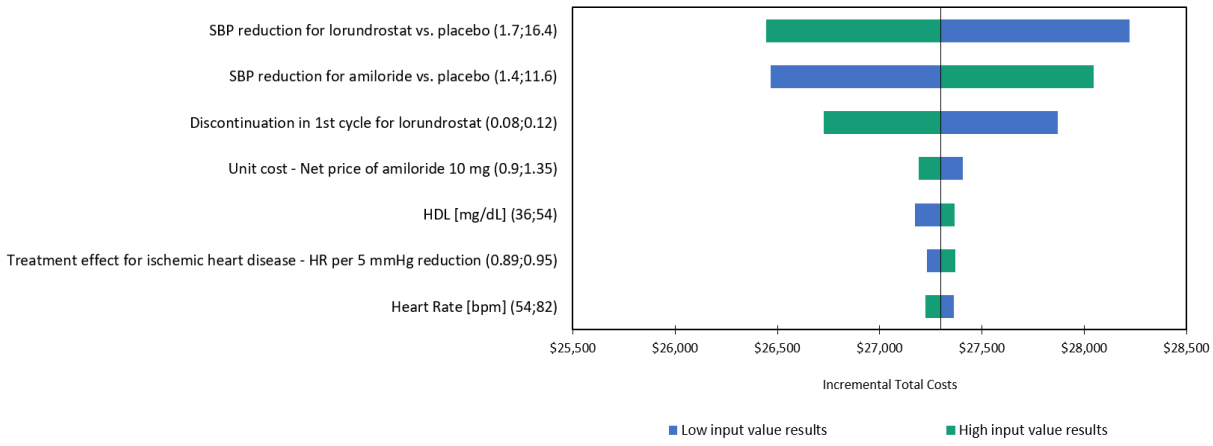


Table E4.12. Tornado Diagram Inputs and Results for Lorundrostat versus Amiloride (Incremental Total Costs)

	Lower Incremental Total Costs	Upper Incremental Total Costs	Lower Input*	Upper Input*
SBP Reduction for Lorundrostat vs. Placebo	$26,400	$28,200	1.7	16.4
SBP Reduction for Amiloride vs. Placebo	$26,500	$28,000	1.4	11.6
Discontinuation in 1st Cycle for Lorundrostat	$26,700	$27,900	0.08	0.12
Unit Cost - Net Price of Amiloride 10 mg	$27,200	$27,400	0.90	1.35
HDL (mg/dL)	$27,200	$27,400	35.92	53.88
Treatment Effect for Ischemic Heart Disease - HR per 5 mmHg Reduction	$27,200	$27,400	0.89	0.95
Heart Rate (beats per minute)	$27,200	$27,400	54.4	81.6

CE: cost-effectiveness, dL: deciliter, HDL: high-density lipoprotein, HR: hazard ratio, mg: milligrams, mm Hg: millimeters of mercury, SBP: systolic blood pressure

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Additionally, we ran a probabilistic sensitivity analysis (PSA) with 1,000 simulations with the proportion of simulations being cost-effective at commonly accepted thresholds in Tables E4.13 and E4.14. We also report the PSA results for each pairwise comparison in Tables E4.15 through E4.20.

Table E4.13. Probabilistic Sensitivity Analysis Cost per evLY Gained Results: Baxdrostat versus Spironolactone, Eplerenone, or Amiloride

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Baxdrostat vs. Spironolactone	0.0%	0.0%	0.0%	0.0%
Baxdrostat vs. Eplerenone	0.0%	0.0%	0.0%	0.3%
Baxdrostat vs. Amiloride	0.0%	0.0%	0.0%	0.2%

evLY: equal value life year

Table E4.14. Probabilistic Sensitivity Analysis Cost per evLY Gained Results: Lorundrostat versus Spironolactone, Eplerenone, or Amiloride

	Cost Effective at $50,000 per evLY Gained*	Cost Effective at $100,000 per evLY Gained*	Cost Effective at $150,000 per evLY Gained*	Cost Effective at $200,000 per evLY Gained*
Lorundrostat vs. Spironolactone	0.0%	0.0%	0.0%	0.3%
Lorundrostat vs. Eplerenone	0.0%	0.0%	0.0%	0.4%
Lorundrostat vs. Amiloride	0.0%	0.0%	0.0%	0.4%

evLY: equal value life year

*Based on placeholder price

Table E4.15. Results of Probabilistic Sensitivity Analysis for Baxdrostat versus Spironolactone,

	Baxdrostat Mean	Spironolactone Mean	Incremental
Costs	$150,000	$123,000	$26,800
QALYs	9.56	9.53	0.03
evLYs	9.56 (95% CrI: 9.20, 9.89)	9.53 (95% CrI: 9.17, 9.87)	0.03 (95% CrI: 0.00, 0.07)
Incremental CE Ratio (evLY)	$877,000		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, QALY: quality-adjusted life year

Table E4.16. Results of Probabilistic Sensitivity Analysis for Baxdrostat versus Eplerenone

	Baxdrostat Mean	Eplerenone Mean	Incremental
Costs	$150,000	$124,000	$25,400
QALYs	9.56	9.54	0.01
evLYs	9.56 (95% CrI: 9.20, 9.89)	9.54 (95% CrI: 9.19, 9.89)	0.01 (95% CrI: -0.04, 0.08)
Incremental CE Ratio	$1,978,000		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, QALY: quality-adjusted life year

Table E4.17. Results of Probabilistic Sensitivity Analysis for Baxdrostat versus Amiloride

	Baxdrostat Mean	Amiloride Mean	Incremental
Costs	$150,000	$123,000	$26,300
QALYs	9.56	9.53	0.03
evLYs	9.56 (95% CrI: 9.20, 9.89)	9.53 (95% CrI: 9.17, 9.86)	0.03 (95% CrI: -0.02, 0.09)
Incremental CE Ratio	$887,000		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, QALY: quality-adjusted life year

Table E4.18. Results of Probabilistic Sensitivity Analysis for Lorundrostat versus Spironolactone

	Lorundrostat Mean	Spironolactone Mean	Incremental
Costs	$151,000	$123,000	$27,800
QALYs	9.54	9.53	0.02
evLYs	9.54 (95% CrI: 9.19, 9.90)	9.53 (95% CrI: 9.17, 9.87)	0.02 (95% CrI: -0.05, 0.09)
Incremental CE Ratio	$1,513,000		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

Table E4.19. Results of Probabilistic Sensitivity Analysis for Lorundrostat versus Eplerenone

	Lorundrostat Mean	Eplerenone Mean	Incremental
Costs	$151,000	$124,000	$26,300
QALYs	9.54	9.54	0.00
evLYs	9.54 (95% CrI: 9.19, 9.90)	9.54 (95% CrI: 9.19, 9.89)	0.00 (95% CrI: -0.08, 0.09)
Incremental CE Ratio	$44,062,000		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, QALY: quality-adjusted life year

Table E4.20. Results of Probabilistic Sensitivity Analysis for Lorundrostat versus Amiloride

	Lorundrostat Mean	Amiloride Mean	Incremental
Costs	$151,000	$123,000	$27,300
QALYs	9.54	9.53	0.02
evLYs	9.54 (95% CrI: 9.19, 9.90)	9.53 (95% CrI: 9.17, 9.86)	0.02 (95% CrI: -0.05, 0.10)
Incremental CE Ratio	$1,566,000		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, QALY: quality-adjusted life year

E5. Scenario Analyses

We conducted scenario analyses that included:

1. The modified societal perspective that included components such as lost productivity from caregivers.
2. Using the same discontinuation assumption for all treatments.
3. Assuming no discontinuation for all treatments.
4. 10 year- and 20-year treatment effect durations (To be conducted in the Evidence Report).
5. Reduced time horizons (e.g., 5 and 10 years) to assess how much of the estimated value derives from cardiovascular and renal events avoided over the long term (To be conducted in the Evidence Report).
6. Minimum (lowest available generic) pricing for the comparator drugs, in place of the median generic price used in the base case (To be conducted in the Evidence Report).

Table E5.1. Scenario Analysis Results (Total Outcomes)

Scenario 1: Modified Societal Perspective					
Treatment	**Drug Cost**	**Total Cost**	**QALYs**	**evLYs**	**LYs**
Baxdrostat	$27,600	$206,000	9.55	9.55	11.87
Lorundrostat	$28,500	$207,000	9.54	9.54	11.86
Spironolactone	$200	$180,000	9.52	9.52	11.83
Eplerenone	$2,000	$181,000	9.54	9.54	11.86
Amiloride	$830	$180,000	9.52	9.52	11.84
Scenario 2: Same Discontinuation for All Treatments					
Treatment	**Drug Cost**	**Total Cost**	**QALYs**	**evLYs**	**LYs**
Baxdrostat	$29,200	$151,000	9.56	9.56	11.88
Lorundrostat	$29,200	$151,000	9.54	9.54	11.86
Spironolactone	$200	$123,000	9.52	9.52	11.83
Eplerenone	$2,000	$124,000	9.54	9.54	11.86
Amiloride	$830	$123,000	9.52	9.52	11.84
Scenario 3: No Discontinuation for All Treatments					
Treatment	**Drug Cost**	**Total Cost**	**QALYs**	**evLYs**	**LYs**
Baxdrostat	$134,000	$249,000	9.88	9.88	12.25
Lorundrostat	$133,000	$250,000	9.80	9.80	12.17
Spironolactone	$1,300	$117,000	9.84	9.84	12.22
Eplerenone	$9,300	$126,000	9.80	9.80	12.16
Amiloride	$3,700	$122,000	9.72	9.72	12.07

evLYs: equal value life years, LYs: life years, QALYs: quality-adjusted life years

Table E5.2. Scenario Analysis Results on Treatment Discontinuation (Clinical Outcomes)

Scenario 2: Same Discontinuation for All Treatments					
Treatment	**MI**	**Stroke**	**CHD**	**HF**	**ESKD**
Baxdrostat	197	150	225	156	11
Lorundrostat	197	151	226	157	11
Spironolactone	198	152	227	159	11
Eplerenone	197	151	226	158	11
Amiloride	198	152	226	159	11
Scenario 3: No Discontinuation for All Treatments					
Treatment	**MI**	**Stroke**	**CHD**	**HF**	**ESKD**
Baxdrostat	184	125	210	132	12
Lorundrostat	187	130	214	138	11
Spironolactone	185	127	212	135	12
Eplerenone	187	130	214	138	11
Amiloride	190	136	218	144	11

evLYs: equal value life years, LYs: life years, QALYs: quality-adjusted life years

Table E5.3. Scenario Analysis Results (Incremental Cost-Effectiveness Ratios)

Scenario 1: Modified Societal Perspective				
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
Baxdrostat	Spironolactone	$819,000	$767,000	$700,000
Baxdrostat	Eplerenone	$2,063,000	$1,941,000	$1,762,000
Baxdrostat	Amiloride	$838,000	$787,000	$715,000
Lorundrostat	Spironolactone	$1,404,000	$1,313,000	$1,201,000
Lorundrostat	Eplerenone	Lower effect, higher cost	Lower effect, higher cost	Lower effect, higher cost
Lorundrostat	Amiloride	$1,479,000	$1,390,000	$1,261,000
Scenario 2: Same Discontinuation for All Treatments				
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
Baxdrostat	Spironolactone	$751,000	$704,000	$642,000
Baxdrostat	Eplerenone	$1,515,000	$1,424,000	$1,294,000
Baxdrostat	Amiloride	$764,000	$718,000	$652,000
Lorundrostat	Spironolactone	$1,322,000	$1,237,000	$1,131,000
Lorundrostat	Eplerenone	$16,455,000	$15,459,000	$14,048,000
Lorundrostat	Amiloride	$1,382,000	$1,298,000	$1,179,000
Scenario 3: No Discontinuation for All Treatments				
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
Baxdrostat	Spironolactone	$4,111,000	$3,849,000	$3,528,000
Baxdrostat	Eplerenone	$1,553,000	$1,454,000	$1,333,000
Baxdrostat	Amiloride	$789,000	$739,000	$677,000
Lorundrostat	Spironolactone	Lower effect, higher cost	Lower effect, higher cost	Lower effect, higher cost
Lorundrostat	Eplerenone	$16,956,000	$15,862,000	$14,539,000
Lorundrostat	Amiloride	$1,436,000	$1,343,000	$1,231,000

evLYs: equal value life years, QALYs: quality-adjusted life years

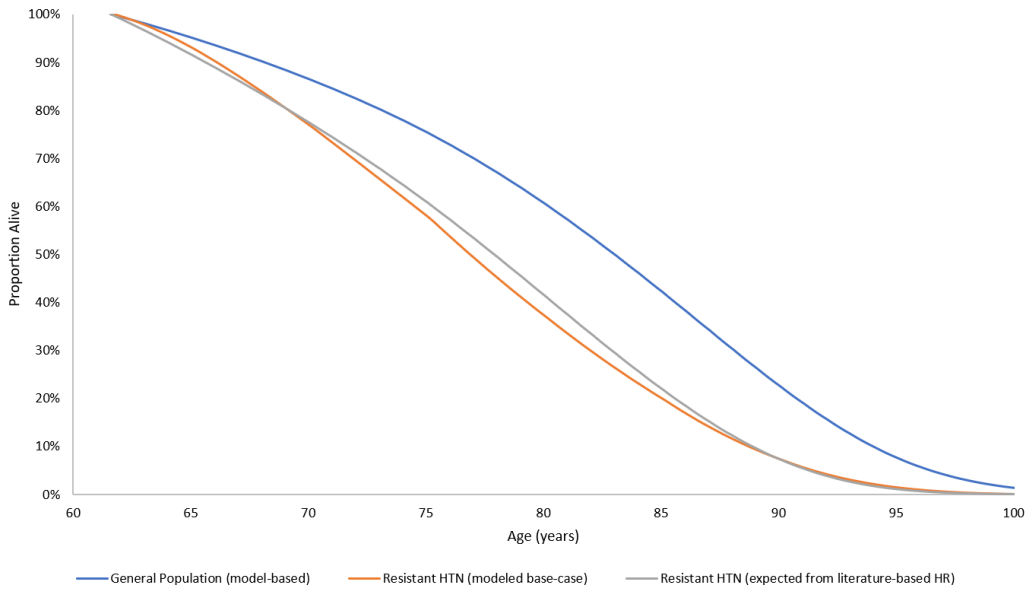
E6. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

To confirm that the model produced overall survival consistent with published evidence for resistant hypertension, modeled life expectancy was compared with two external benchmarks (Figure E6.1). We compared undiscounted life expectancy from the modelled hypertension population to the general population over the same lifetime horizon from a starting age of 61.6 years. The general population yielded a life expectancy of 20.5 years. Additionally, we applied an all-cause mortality hazard ratio of 1.76 based on the literature for resistant hypertension to the general population, which resulted in a life expectancy of 16.0 years.[156] The model's resistant hypertension base-case cohort resulted in 15.7 years, corresponding to a survival deficit of 4.8 years versus the general population and a modest 0.4 years versus the literature-based resistant hypertension, the latter indicating that mortality in the model was slightly more conservative than the literature-based estimate.

Figure E6.1. Survival Curves of Resistant Hypertension and General Population



Prior Economic Models

Over a lifetime horizon, the model projected approximately 11.8 LYs and 9.5 QALYs per patient (about 15 and 12, respectively, undiscounted), with near-identical totals across all five treatments because the interventions differed only modestly in systolic blood-pressure lowering. These projections were consistent with comparable US cost-effectiveness analyses of hypertension conducted over a lifetime horizon at a 3% discount rate. The SPRINT-based analysis of intensive versus standard blood-pressure management in 68-year-old high-risk adults (Richman et al. 2016), projected 9.6-10.5 QALYs and the Medicare triple-combination-therapy analysis in adults aged 65 and older (Wang et al. 2021), projected total QALYs in the range of 6.4 to 8.8.[65,71] We had a slightly younger starting cohort (mean age around 62), and even though our modeling methods and choices differed, our results were comparable to these previous models.

Geisler et al. (2012) was the original model that used this assessment's model schematic in a population of resistant hypertension, and they reported a median survival of 17.1 years for standard of care with a cohort entering their model at 58 years old.[62] While a different measure of the central tendency, our mean undiscounted 16 life-years was similar and consistent given our older starting cohort (62 years old). Additionally, McFarlane et al. (2025) was a recent economic analysis that adapted the Geisler et al. framework in an uncontrolled hypertension population and reported 15.30 QALYs for standard of care, but that analysis used a younger cohort (age 55) and, a 1.5% discount rate.[63] Applying those same starting parameters in our model, we obtained estimates of approximately 13.06 QALYs, a difference that seems reasonable given the different approach we used to calculate QALYs.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

ICER's methods for estimating potential budget impact are described in detail in the Value Assessment Framework. The intent of our approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility.

As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent five-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2025-2026, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $821 million per year for new drugs.