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Drug Class Literature Scan: Combination Antihypertensive Drugs, Calcium Channel Blockers and Oral Beta-Blockers

Date of Review: August 2026

Literature Search: 1/1/2015-5/15/2026
Date of Last Review: Combination Antihypertensives (July 2015)
Calcium Channel Blockers (July 2015)
Beta-Blockers, Oral (December 2022)

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This review looks at recent evidence for the effectiveness and safety of 2 classes of medicines used to treat hypertension.
- Hypertension, or high blood pressure, is often times a life-long medical condition where the force of blood pushing against the blood vessels is too high. This makes the heart work harder than normal to pump blood throughout the body. Over time, this extra strain can damage the blood vessels and increase the risk of having a heart attack, stroke, heart failure, or kidney disease.
- Most people with high blood pressure do not have symptoms. The risk of high blood pressure increases with advancing age, being overweight, family history of high blood pressure, a diet high in salt, not being physically active, smoking, and drinking too much alcohol.
- High blood pressure can be diagnosed when your provider checks it during a medical checkup. If the blood pressure reading is greater than 130/80 millimeters of mercury (mm Hg) on 2 or more readings taken on separate occasions, it is considered too high and should be treated with medicine. The top number (systolic) is the pressure inside the arteries when the heart is contracting. The bottom number (diastolic) is the pressure inside the arteries when the heart is relaxed.
- People with very high blood pressure (usually 180/120 mm Hg or higher) can have severe headaches, chest pain, dizziness, blurred vision, or an abnormal heart rhythm. If people have these symptoms, they should immediately seek medical care.
- There are many different medicines used to treat high blood pressure including calcium channel blockers and beta-blockers. Some people may need to take two or more blood pressure medicines to keep their blood pressure within normal range (less than 130/80 mm Hg).
- Calcium channel blockers include amlodipine, nifedipine, and diltiazem These medicines relax the muscles of the blood vessels and slow the heart rate. Calcium channel blockers are recommended as one of the first-line treatments for high blood pressure.
- Beta-blockers include atenolol, metoprolol, carvedilol, and propranolol. These medicines help the heart to beat slower and with less force. Beta-blockers also relax the blood vessels to decrease blood pressure. If people are using 3 medicines to manage their blood pressure and have not reached their target goal, a beta-blocker may be added to their other medicines. Beta-blockers are also used in people after they have had a heart attack or if they have heart failure.

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- Calcium channel blockers and beta-blockers are preferred in pregnant women with high blood pressure because they have been proven to be safe to the baby and the mother.
- Oregon Health Plan (OHP) pays for these calcium channel blockers: amlodipine, nicardipine, nifedipine, diltiazem, and verapamil. Several beta-blockers are also paid for by OHP including acebutolol, atenolol, carvedilol, labetalol, metoprolol succinate, metoprolol tartrate, and propranolol. Providers must submit documentation to OHP if other beta-blockers or calcium channel blockers are prescribed. This process is called prior authorization.

Conclusions:

- Since the last review of beta-blockers and CCBs, 3 high-quality systematic reviews[1-3] and 4 guidelines[4-7] have been published.
- The objective of a 2022 Cochrane review was to determine whether calcium channel blockers (CCBs) used as first-line therapy for hypertension are different from other classes of antihypertensive drugs in reducing the incidence of major adverse cardiovascular events (MACE).[1] For the treatment of hypertension, there is moderate certainty evidence that diuretics reduce the incidence of MACE and congestive heart failure (CHF) events more than CCBs.[1] There is low to moderate certainty evidence that CCBs probably reduce the incidence of MACE more than beta-blockers.[1] There is low to moderate certainty evidence that CCBs reduce the incidence of stroke when compared to angiotensin converting enzyme (ACE) inhibitors and reduce myocardial infarction (MI) events when compared to angiotensin II receptor blockers (ARBs) but increased CHF events when compared to ACE inhibitors and ARBs.[1]
- A 2018 Cochrane review evaluated the benefits and harms of first-line renin angiotensin system (RAS) inhibitors compared to other first-line antihypertensive drugs in people with hypertension.[2] All-cause death is similar for first-line RAS inhibitors and first-line CCBs, thiazides and beta-blockers (moderate certainty evidence).[2] First-line thiazides reduced the risk heart failure and stroke more than first-line RAS inhibitors (moderate certainty evidence).[2] First-line CCBs increased heart failure but decreased stroke compared to first-line RAS inhibitors (moderate certainty evidence).[2] Low certainty evidence suggests that first-line RAS inhibitors reduced stroke and total cardiovascular (CV) events compared to first-line beta-blockers.[2]
- A 2018 Cochrane review assessed the effects of antihypertensive drug treatments for women with mild to moderate hypertension during pregnancy.[3] Moderate certainty evidence shows that antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension.[3] Based on low to moderate certainty evidence, the effect on other clinically important outcomes (i.e., proteinuria, preeclampsia, maternal death, impaired fetal growth, fetal death) remains unclear.[3] Moderate certainty evidence shows that If antihypertensive drugs are used, beta-blockers and CCBs appear to be more effective than the alternatives (i.e., methyldopa) for preventing severe hypertension.[3]
- The 2025 report of the American College of Cardiology/American Heart Association (ACC/AHA) joint committee on clinical practice guidelines for management of hypertension replaced 2017 guidance.[4] The blood pressure (BP) treatment goal is less than 130/80 mm Hg for all adults, with additional considerations for those who require institutional care, have a limited predicted lifespan, or are pregnant.[4] Initiation of medication therapy to lower BP in addition to lifestyle interventions is recommended for all adults with average BP greater than or equal to 140/90 mm Hg and/or for selected adults with average BP greater than or equal to 130/80 mm Hg who have clinical cardiovascular disease (CVD), previous stroke, diabetes, chronic kidney disease (CKD), or increased 10-year predicted CV risk greater than 7.5%.[4] Strong evidence from clinical trials supports 4 classes of first-line agents compared with placebo (thiazide-type diuretics, long-acting dihydropyridine CCBs, ACE inhibitors, and ARBs) due to their favorable profiles for BP lowering, CVD prevention, and tolerability.[4] Beta-blockers were less effective than first-line antihypertensive classes in preventing stroke and had a less favorable side effect profile; therefore, they should be reserved for adults with compelling indications (i.e., post-MI, heart failure).[4] Descriptions of the ACC/AHA classes of recommendations (COR) and level of evidence (LOE) are summarized in **Table 1.** Specific recommendations for the use of CCBs and beta-blockers in treating hypertension include:
    - For adults initiating antihypertensive drug therapy, thiazide-type diuretics, long acting dihydropyridine CCB, and ACE inhibitor or ARB are recommended as first-line therapy to prevent CVD. (COR: 1; LOE: A).[4]

- In adults with Stage 2 hypertension (systolic blood pressure [SBP] ≥ 140 mm Hg and diastolic blood pressure [DBP] ≥ 90 mm Hg) initiation of antihypertensive drug therapy with 2 first-line agents of different classes, ideally in a single-pill combination, is recommended to improve BP control and adherence (COR: 1; LOE: B-R).[4]
- In adults with Stage 1 hypertension (SBP 130-139 mm Hg and DBP 80-89 mm Hg), initiation of antihypertensive drug therapy with a single first-line antihypertensive drug is reasonable, with dosage titration and sequential addition of other agents as needed to achieve BP control (COR: 2a; LOE: C-EO).[4]
- In adults with uncontrolled hypertension who cannot tolerate or have contraindications to a mineralocorticoid receptor antagonist (MRA), the addition of one of the following agents or classes – amiloride, beta-blockers, alpha-blockers, central sympatholytic drugs, dual endothelin receptor antagonist, or direct vasodilator – is reasonable to control BP. (COR: 2a; LOE: B-NR)[4]

- One of the most important changes in the European Society of Cardiology (ESC) 2024 hypertension guidance is the focus on evidence related to CVD outcomes of BP-lowering interventions rather than BP lowering alone.[5] The major drug classes with robust evidence for BP-mediated reduction in CVD events are ACE inhibitors, ARBs, dihydropyridine CCBs, diuretics (thiazides and thiazide-like diuretics such as hydrochlorothiazide, chlorthalidone, and indapamide), and beta-blockers.[5] The first 4 are recommended as first-line options for starting hypertension treatment in the general population.[5] Beta-blockers can be added preferentially in circumstances such as in the presence of angina or heart failure, after MI, or for controlling heart rate, where they are the cornerstone of therapy.[5] However, beta-blockers are less effective than ACE inhibitors, ARBs, CCBs, or diuretics at preventing stroke, and have a higher discontinuation rate due to side effects.[5] The ESC pharmacologic recommendations for treating hypertension are presented in **Table 2**.
- The Veterans Affairs/Department of Defense (VA/DoD) recommendations for management of hypertension were updated in 2020.[6] This guideline working group, on the basis of their review of the literature, defined hypertension as an SBP of 130 mm Hg or greater or a DBP of 90 mm Hg or greater.[6] Evidence supports the use of a thiazide-type diuretic, a CCB, or either an ACE inhibitor or an ARB as primary pharmacologic therapy for hypertension.[6] The effects of the various antihypertensive drug classes on reducing composite CV outcomes, and not just differences in BP–lowering effect, were the focus of the recommendation.[6] The VA/DoD guidance is similar to the ACC/AHA and ESC guidance. Specific goals of therapy and pharmacologic treatment recommendations are summarized in **Table 3**.
- The National Institute for Health and Care Excellence (NICE) published guidance for hypertension management in adults in 2019.[7] The recommendations align with other organizations and are summarized below. Calcium channel blockers are recommended as first line agents for treatment of hypertension and beta-blockers are reserved for people with resistant hypertension.[7]
- Recent Food and Drug Administration (FDA)-approved formulations and indications:
  - 12/2025: A 10 mg/mL oral solution of LOPRESSOR (metoprolol) received FDA approval, indicated for the treatment of adults with hypertension, in the long-term treatment of angina pectoris, and the in the treatment of hemodynamically stable patients with definite or suspected MI to reduce the risk of CV mortality when used in conjunction with intravenous metoprolol therapy.[8] The manufacturer did not conduct new studies for this new formulation and relied on the FDA's finding of safety and effectiveness of metoprolol tablets.
  - 7/2025: The FDA approved SDAMLO, new unit-dose oral powder formulation of amlodipine.[9] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[9] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications.
  - 6/2025: A new triple combination oral tablet, WIDAPLIK (telmisartan/amlodipine/indapamide) received FDA-approval, indicated for the treatment of hypertension in adults [10] The product is available in 3 strengths containing telmisartan, amlodipine, and indapamide in the following combinations: 10 mg/1.25 mg/0.625 mg; 20 mg/2.5 mg/1.25 mg; and 40 mg/5 mg/2.5 mg.[10] The efficacy of WIDAPLIK in lowering blood pressure was evaluated in a randomized study designed to evaluate the efficacy and safety of two doses of WIDAPLIK (10 mg/1.25 mg/0.625 mg and 20 mg/2.5 mg/1.25 mg)

compared to placebo (Study 1, NCT04518306) and in a randomized study designed to evaluate the efficacy and safety of WIDAPLIK (40 mg/5 mg/2.5 mg) as compared to each of its two-drug combinations at the same doses (Study 2, NCT04518293).[10] In both studies, triple therapy with telmisartan/amlodipine/indapamide showed statistically significant greater reductions in BP compared to placebo or dual therapy.[10] Study details are results are presented below.

- 2/2022: The FDA approved NORLIQVA, a 1 mg/mL oral solution formulation of amlodipine.[11] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[11] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications.
- 12/2019: A new medication, CONJPRI, levamlodipine oral tablet was FDA-approved to treat hypertension in adults and pediatric patients aged 6 years an older either alone or in combination with other antihypertensive agents.[12] Levamlodipine is an active isomer of amlodipine.[12] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications.
- 7/2019: The FDA approved KATERZIA, new 1 mg/mL oral solution formulation of amlodipine.[13] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[13] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications.
- 6/2106: The FDA approved an oral tablet combination product, BYVALSON (nebivolol/valsartan 5mg/80mg), indicated for the treatment of hypertension.[14] BYVALSON was studied in a Phase 3, double-blind, placebo-controlled, dose-escalating, 8-week study in 4,161 patients with Stage 1 or 2 hypertension.[14] Treatment with BYVALSON 5 mg/ 80 mg for 4 weeks resulted in placebo-adjusted reductions from baseline in SBP and DBP of -8.3 and -7.2 mmHg, respectively.[14] Treatment with BYVALSON 5 mg/ 80 mg resulted in greater reductions in SBP and DBP than did treatment with nebivolol 5 mg alone ($p<0.0001$ for both SBP and DBP) or valsartan 80 mg, alone ($p=0.0007$ for SBP and $p<0.0001$ for DBP).[14] During the 4-week period, the overall incidence of adverse events on therapy with BYVALSON 5 mg/ 80 mg was similar to placebo and the individual components (nebivolol 5 mg and valsartan 80 mg).[14]

- Recent FDA safety revisions to manufacturers prescribing information are presented in **Table 6**.

Recommendations:

- Maintain LOPRESSOR (metoprolol) oral solution, SDAMLO (amlodipine) oral powder, WIDAPLIK (telmisartan/amlodipine/indapamide) tablets, NORLIQVA (amlodipine) oral solution, CONJPRI (levamlodipine) tablets, KATERZIA (amlodipine)oral solution, and BYVALSON (nebivolol/valsartan) tablets as non-preferred on the Preferred Drug List (PDL). Make nimodipine capsules preferred and the brand name NIMOTOP capsules and solution non-preferred.
- No other PDL changes are recommended based on review of recent evidence.
- Review drug costs in Executive Session.

Summary of Prior Reviews and Current Policy

- The beta blocker class was last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the August 2022 meeting. All of the beta blockers reviewed were effective in the treatment of hypertension, but there was no evidence of differences between beta blockers for BP control, survival, or quality of life. Three beta blockers, bisoprolol, carvedilol, and extended-release metoprolol succinate, have been shown to reduce mortality and morbidity in patients with heart failure with reduced ejection fraction (HFrEF).[15] A beta blocker without intrinsic sympathomimetic activity such as extended-release metoprolol succinate, bisoprolol, or carvedilol, should be initiated in the setting of an acute MI to manage atrial fibrillation.[16] Labetalol is the preferred oral beta-blocker

for managing gestational hypertension.[17] Finally, propranolol has demonstrated efficacy in migraine prophylaxis[18] and treatment of infantile hemangioma.[19,20] Topical timolol is also effective in treatment of thin (less than 1 mm), superficial infantile hemangioma.[20]

- After reviewing drug costs in the executive session, propranolol SA 24-hour capsules, generic oral propranolol solution, and nadolol tabs were designated as preferred on the PDL and open access for HEMANGEL (propranolol) oral solution for patients up to 6 months of age with infantile hemangioma was approved.
- **Appendix 1** summarizes the current preferred beta blocker status on the PDL which includes: acebutolol, atenolol, carvedilol, labetalol, metoprolol succinate, metoprolol tartrate, and propranolol.
- Calcium channel blockers (CCBs) and fixed dose combinations of antihypertensives were last reviewed by the P & T Committee at the July 2015 meeting. There was insufficient evidence comparing relative efficacy and safety of CCBs with other CCBs. In 2015, guidelines recommended CCBs as a first-line treatment option for hypertension. There was insufficient evidence comparing a fixed-dose antihypertensive combination product containing a CCB with the respective drugs taken concomitantly as separate formulations for the treatment of hypertension. The committee agreed to maintain at least 2 preferred dihydropyridine CCBs, including amlodipine, and maintain at least 1 preferred extended-acting and immediate-release formulation of diltiazem and verapamil on the PDL.
- **Appendix 1** summarizes the current preferred CCB status on the PDL which includes: amlodipine, nicardipine, nifedipine, diltiazem, and verapamil. Preferred combination antihypertensives include amlodipine/olmesartan, benazepril/hydrochlorothiazide (HCTZ), enalapril/HCTZ, lisinopril/HCTZ, losartan/HCTZ, olmesartan/amlodipine/HCTZ, and telmisartan/HCTZ. Nonpreferred agents are subject to the standard non-preferred prior authorization criteria.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane Review: Calcium Channel Blockers Versus Other Classes Of Drugs For Hypertension (2022)

The objective of this review was to determine whether CCBs used as first-line therapy for hypertension are different from other classes of antihypertensive drugs in reducing the incidence of MACE.[1] Literature was searched through September 1, 2020 for RCTs comparing first-line CCBs with other antihypertensive classes, with at least 100 randomized hypertensive participants and a follow-up of at least 2 years.[1] This update included a total of 23 RCTs (18 dihydropyridines, 4 non-dihydropyridines, 1 not specified) with 153,849 participants with hypertension.[1]

As compared to diuretics, CCBs probably increased the incidence of MACE (risk ratio [RR] 1.05, 95% confidence interval [CI] 1.00 to 1.09, P = 0.03) and increased CHF events (RR 1.37, 95% CI 1.25 to 1.51, moderate-certainty evidence).[1] As compared to beta-blockers, CCBs reduced the incidence of the following outcomes:

MACE (RR 0.84, 95% CI 0.77 to 0.92), stroke (RR 0.77, 95% CI 0.67 to 0.88, moderate-certainty evidence), and CV mortality (RR 0.90, 95% CI 0.81 to 0.99, low-certainty evidence).[1] As compared to ACE inhibitors, CCBs reduced the incidence of stroke (RR 0.90, 95% CI 0.81 to 0.99, low-certainty evidence) and increased CHF events (RR 1.16, 95% CI 1.06 to 1.28, low-certainty evidence).[1] As compared to ARBs, CCBs reduced the incidence of MI (RR 0.82, 95% CI 0.72 to 0.94, moderate-certainty evidence) and increased CHF events (RR 1.20, 95% CI 1.06 to 1.36, low-certainty evidence).[1]

In summary, for the treatment of hypertension, there is moderate certainty evidence that diuretics reduce the incidence of MACE and CHF events more than CCBs.[1] There is low to moderate certainty evidence that CCBs probably reduce the incidence of MACE more than beta-blockers.[1] There is low to moderate certainty evidence that CCBs reduce the incidence of stroke when compared to ACE inhibitors and reduce MI events when compared to ARBs but increased CHF events when compared to ACE inhibitors and ARBs.[1] Many of the differences found in the current review are not robust, and further trials might change the conclusions.[1]

Cochrane Review: First-Line Drugs Inhibiting The Renin Angiotensin System Versus Other First-Line Antihypertensive Drug Classes For Hypertension (2018)

This review evaluated the benefits and harms of first-line RAS inhibitors compared to other first-line antihypertensive drugs in people with hypertension.[2] Literature was searched through November 2017 for active-controlled, double-blinded RCTs with at least 6 months follow-up in people with elevated BP greater than or equal to 130/85 mmHg, which compared first-line RAS inhibitors with other first-line antihypertensive drug classes and reported morbidity and mortality or BP outcomes.[2] People with proven secondary hypertension were excluded.[2] This update includes 3 new RCTs, totaling 45 RCTs in all, involving 66,625 participants, with a mean age of 66 years.[2] Much of the evidence for the key outcomes is dominated by a small number of large RCTs at low risk for most sources of bias.[2] Imbalances in the added second-line antihypertensive drugs in some of the studies were important enough to downgrade the quality of the evidence.[2] Primary outcomes were all-cause death, fatal and non-fatal stroke, fatal and non-fatal MI, fatal and non-fatal CHF requiring hospitalizations, total CV events (fatal and non-fatal stroke, fatal and non-fatal MI and fatal and non-fatal CHF requiring hospitalization), and end-stage renal failure (ESRF).[2] Secondary outcomes were systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR).[2]

Compared with first-line CCBs, moderate-certainty evidence showed that first-line RAS inhibitors decreased heart failure (35,143 participants in 5 RCTs, RR 0.83, 95% CI 0.77 to 0.90, absolute risk reduction [ARR] 1.2%), and that they increased stroke (34,673 participants in 4 RCTs, RR 1.19, 95% CI 1.08 to 1.32, absolute risk increase [ARI] 0.7%).[2] Moderate-certainty evidence showed that first-line RAS inhibitors and first-line CCBs did not differ for all-cause death (35,226 participants in 5 RCTs, RR 1.03, 95% CI 0.98 to 1.09); total CV events (35,223 participants in 6 RCTs, RR 0.98, 95% CI 0.93 to 1.02); and total MI events (35,043 participants in 5 RCTs, RR 1.01, 95% CI 0.93 to 1.09).[2] Low-certainty evidence suggests they did not differ for the incidence of ESRF (19,551 participants in 4 RCTs, RR 0.88, 95% CI 0.74 to 1.05).[2]

Compared with first-line thiazides, moderate-certainty evidence showed that first-line RAS inhibitors increased heart failure (24,309 participants in 1 RCT, RR 1.19, 95% CI 1.07 to 1.31, ARI 1.0%), and increased stroke (24,309 participants in 1 RCT, RR 1.14, 95% CI 1.02 to 1.28, ARI 0.6%).[2] Moderate-certainty evidence showed that first-line RAS inhibitors and first-line thiazides did not differ for all-cause death (24,309 participants in 1 RCT, RR 1.00, 95% CI 0.94 to 1.07); total CV events (24,379 participants in 2 RCTs, RR 1.05, 95% CI 1.00 to 1.11); and total MI events (24,379 participants in 2 RCTs, RR 0.93, 95% CI 0.86 to 1.01).[2] Low-certainty evidence suggests they did not differ for the incidence of ESRF (24,309 participants in 1 RCT, RR 1.10, 95% CI 0.88 to 1.37).[2]

Compared with first-line beta-blockers, low-certainty evidence suggests that first-line RAS inhibitors decreased total CV events (9239 participants in 2 RCTs, RR 0.88, 95% CI 0.80 to 0.98, ARR 1.7%), and decreased stroke (9193 participants in 1 RCT, RR 0.75, 95% CI 0.63 to 0.88, ARR 1.7%). Low-certainty evidence suggests that first-line RAS inhibitors and first-line beta-blockers did not differ for all-cause death (9193 participants in 1 RCT, RR 0.89, 95% CI 0.78 to 1.01); HF (9193

participants in 1 RCT, RR 0.95, 95% CI 0.76 to 1.18); and total MI events (9239 participants in 2 RCTs, RR 1.05, 95% CI 0.86 to 1.27).[2] There is no information about non-fatal serious adverse events, as none of the trials reported this outcome.[2]

In summary, all-cause death is similar for first-line RAS inhibitors, first-line CCBs, thiazides and beta-blockers (moderate certainty evidence).[2] First-line thiazides caused less heart failure and stroke than first-line RAS inhibitors (moderate certainty evidence).[2] First-line CCBs increased heart failure but decreased stroke compared to first-line RAS inhibitors (moderate certainty).[2] Low-quality evidence suggests that first-line RAS inhibitors reduced stroke and total CV events compared to first-line beta-blockers.[2]

Cochrane Review: Antihypertensive Drug Therapy For Mild To Moderate Hypertension During Pregnancy (2018)

This review assessed the effects of antihypertensive drug treatments for women with mild to moderate hypertension during pregnancy.[3] Literature was searched through September 2017 for RCTs evaluating any antihypertensive drug treatment for mild to moderate hypertension during pregnancy, defined as SBP 140 to 169 mmHg and/or DBP 90 to 109 mmHg.[3] Comparisons were of one or more antihypertensive drug(s) with placebo, with no antihypertensive drug, or with another antihypertensive drug, and where treatment was planned to continue for at least 7 days.[3] Sixty-three trials met inclusion criteria (data from 58 trials, 5909 women), with moderate to high risk of bias overall.[3]

- Antihypertensive Drug Versus Placebo/No Antihypertensive Drug (31 Trials, 3485 Women)

Primary outcomes: moderate-certainty evidence suggests that use of antihypertensive drug(s) probably halves the risk of developing severe hypertension (RR 0.49; 95% confidence interval (CI) 0.40 to 0.60; 20 trials, 2558 women), but may have little or no effect on the risk of proteinuria/pre-eclampsia (average RR 0.92; 95% CI 0.75 to 1.14; 23 trials, 2851 women; low-certainty evidence).[3] Moderate-certainty evidence also shows that antihypertensive drug(s) probably have little or no effect in the risk of total reported fetal or neonatal death (including miscarriage) (average RR 0.72; 95% CI 0.50 to 1.04; 29 trials, 3365 women), small-for-gestational-age babies (RR 0.96; 95% CI 0.78 to 1.18; 21 trials, 2686 babies) or preterm birth less than 37 weeks (average RR 0.96; 95% CI 0.83 to 1.12; 15 trials, 2141 women).[3]

Secondary outcomes: the effect of antihypertensive drug(s) is uncertain on the risk of maternal death, severe pre-eclampsia , or eclampsia, or impaired long-term growth and development of the baby in infancy and childhood , because the certainty of this evidence is very low.[3] There may be little or no effect on the risk of changed/stopped drugs due to maternal side-effects, or admission to neonatal or intensive care nursery (low-certainty evidence). There is probably little or no difference in the risk of elective delivery (moderate-certainty evidence).[3]

- Antihypertensive Drug Versus Another Antihypertensive Drug (29 Trials, 2774 Women)

Primary outcomes: beta-blockers and CCBs together in the meta-analysis appear to be more effective than methyldopa in avoiding an episode of severe hypertension (RR 0.70; 95% CI 0.56 to 0.88; 11 trials, 638 women).[3] There was also an increase in this risk when other antihypertensive drugs were compared with CCBs (RR 1.86; 95% CI 1.09 to 3.15; 5 trials, 223 women), but no evidence of a difference when methyldopa and CCBs together were compared with beta-blockers (RR 1.18, 95% CI 0.95 to 1.48; 10 trials, 692 women).[3] No evidence of a difference in the risk of proteinuria/pre-eclampsia was found when alternative drugs were compared with methyldopa (average RR 0.78; 95% CI 0.58 to 1.06; 11 trials, 997 women), with CCBs (average RR: 1.24, 95% CI 0.70 to 2.19; 5 trials, 375 women), or with beta-blockers (average RR 1.21, 95% CI 0.88 to 1.67; 12 trials, 1107 women).[3]

For the babies, there was no evidence of a difference in the risk of total reported fetal or neonatal death (including miscarriage) when comparing other antihypertensive drugs with methyldopa (average RR 0.77, 95% CI 0.52 to 1.14; 22 trials, 1791 babies), with CCBs (average RR 0.90, 95% CI 0.52 to 1.57; 9 trials,

700 babies), or with beta-blockers (average RR: 1.23, 95% CI 0.81 to 1.88; 19 trials, 1652 babies); nor in the risk for small-for-gestational age in the comparison with methyldopa (average RR 0.79, 95% CI 0.52 to 1.20; 7 trials, 597 babies), with CCBs (average RR 1.05, 95% CI 0.64 to 1.73; 4 trials, 200 babies), or with beta-blockers (average RR 1.13, 95% CI 0.80 to 1.60; 7 trials, 680 babies).[3] No evidence of an overall difference among groups in the risk of preterm birth (less than 37 weeks) was found in the comparison with methyldopa (average RR: 0.91; 95% CI 0.68 to 1.22; 11 trials, 835 women), with CCBs (average RR 0.85, 95% CI 0.59 to 1.23; 6 trials, 330 women), or with beta-blockers (average RR 1.22, 95% CI 0.90 to 1.66; 9 trials, 806 women).[3]

In summary, moderate certainty evidence shows that antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension.[3] Based on low to moderate certainty evidence, the effect on other clinically important outcomes (proteinuria, preeclampsia, maternal death, impaired fetal growth, fetal death) remains unclear.[3] Moderate certainty evidence shows that If antihypertensive drugs are used, beta-blockers and CCBs appear to be more effective than the alternatives (i.e. methyldopa) for preventing severe hypertension.[3]

After review, 42 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), network meta-analysis, comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

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 (2025)

This 2025 update replaces the 2017 guidance. High BP is the most prevalent and modifiable risk factor for the development of CVD, including coronary artery disease, CHF, atrial fibrillation, stroke, dementia, CKD, and all-cause mortality.[4] The overarching BP treatment goal is less than 130/80 mm Hg for all adults, with additional considerations for those who require institutional care, have a limited predicted lifespan, or are pregnant.[4] For a given BP level, absolute risk for cardiovascular disease (CVD) varies according to age, sex, and presence of CVD or CVD risk factors.[4] Therefore, the decision to initiate antihypertensive treatment should be based on BP level and risk.[4] Based on BP level alone, all adults with hypertension benefit from antihypertensive therapy at a threshold greater than or equal to 140/90 mm Hg.[4] Adults with hypertension and clinical CVD (coronary heart disease, stroke, or CHF) are at increased risk for CVD events and benefit from antihypertensive therapy at a lower BP threshold of 130/80 mm Hg or greater to prevent recurrent events.[4] Among adults without clinical CVD, identification of patients at increased risk for CVD selects those who derive greatest benefit from antihypertensive therapy at a threshold of 130/80 mm Hg or greater.[4] Adults with hypertension are defined at increased risk if they have diabetes, CKD, or an estimated 10-year CVD risk of 7.5% and higher, according to PREVENT (Predicting Risk of CVD EVENTs).[4]

PREVENT was derived from contemporary data from 3.2 million individuals with baseline examinations from 1992 to 2022 and included a diverse sample of racial and ethnic groups.[4] PREVENT estimates risk for total CVD (MI, stroke, and heart failure), which is especially relevant as trials evaluating antihypertensive therapies and BP thresholds have focused on major adverse cardiovascular events (MACE) as the primary outcome.[4] PREVENT incorporates measures of kidney function, as CKD is an important end-organ manifestation of hypertension and is associated with higher CVD risk.[4] PREVENT includes the integration of place-based social risk using the social deprivation index (SDI), as the burden of hypertension is higher among those who reside in neighborhoods with higher deprivation.[4]

For all adults with stage 2 hypertension, the initiation of antihypertensive drug therapy with 2 first-line agents of different classes in a single-pill, fixed-dose combination is preferred over 2 separate pills to improve adherence and reduce time to achieve BP control.[4] Severe hypertension in nonpregnant individuals,

defined as BP greater than 180/120 mm Hg, without evidence of acute target organ damage, should be evaluated and treated in the outpatient setting with initiation, reinstitution, or intensification of oral antihypertensive medications in a timely manner.[4]

When initiating pharmacological therapy, primary consideration should be given to comorbidities (e.g., coronary artery disease, heart failure, stroke, diabetes, CKD) for which specific BP-lowering medication classes are indicated.[4] Strong RCT evidence supports 4 classes of first-line agents compared with placebo (thiazide-type diuretics, long-acting dihydropyridine CCBs, ACE inhibitors, and ARBs) due to their favorable profiles for BP lowering, CVD prevention, and tolerability.[4] Beta-blockers were less effective than first-line antihypertensive classes in preventing strokes and had a less favorable side effect profile; therefore, they should be reserved for adults with compelling indications (i.e., post-MI, heart failure).[4] American Heart Association guidance (2022) recommends that in patients with hypertension and HFrEF, even if asymptomatic, use 1 of the 3 beta-blockers proven to reduce mortality and hospitalizations (bisoprolol, carvedilol, metoprolol succinate) is preferred.[15] Throughout the ACC/AHA guideline, the term thiazide-type diuretic is used to collectively refer to HCTZ, chlorthalidone, and indapamide.[4] The interchangeability of thiazide-type and -like agents remains a debated topic.[4]

ACC/AHA pharmacologic recommendations that specifically cite beta-blockers and CCBs are summarized below. Descriptions of the recommendations and level of evidence are summarized afterward in **Table 1.**

- For adults initiating antihypertensive drug therapy, thiazide-type diuretics, long acting dihydropyridine CCB, and ACE inhibitor or ARB are recommended as first-line therapy to prevent CVD. (COR: 1; LOE: A).[4]
- In adults with Stage 2 hypertension (SBP $\geq$ 140 mm Hg and DBP $\geq$ 90 mm Hg) initiation of antihypertensive drug therapy with 2 first-line agents of different classes, ideally in a single-pill combination, is recommended to improve BP control and adherence (COR: 1; LOE: B-R).[4]
- In adults with Stage 1 hypertension (SBP 130-139 mm Hg and DBP 80-89 mm Hg), initiation of antihypertensive drug therapy with a single first-line antihypertensive drug is reasonable, with dosage titration and sequential addition of other agents as needed to achieve BP control (COR: 2a; LOE: C-EO).[4]
- In adults with hypertension, simultaneous use of an ACE inhibitor, ARB, and/or renin inhibitor in combination is not recommended due to the potential for harm. (COR: Harm; LOE: A).[4]
- In adults with uncontrolled hypertension who cannot tolerate or have contraindications to a MRA, the addition of one of the following agents or classes – amiloride, beta-blockers, alpha-blockers, central sympatholytic drugs, dual endothelin receptor antagonist, or direct vasodilator – is reasonable to control BP. (COR: 2a; LOE: B-NR)[4]

Table 1. Descriptions for the Strength of Recommendations and Level of Evidence in ACC/AHA Guidance[4]

Class of Recommendation	**Class 1 (Strong)**	**Class 2a (Moderate)**	**Class 2b (Weak)**	**Class 3 - No Benefit (Moderate)**	**Class 3 - Harm (Strong)**
Benefit/Risk Ratio	Benefit >>> Risk	Benefit >> Risk	Benefit $\geq$ Risk	Benefit = Risk	Risk > Benefit
Level of Evidence	**A**	**B-R (Randomized)**	**Level B-NR (Non-randomized)**	**Level C-LD (Limited Data)**	**Level C-EO (Expert Opinion)**
Source	• High-quality evidence from more than 1 RCT • Meta-analyses of high-quality RCTs	• Moderate-quality evidence from 1 or more RCTs	• Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies,	• Randomized or nonrandomized observational or registry studies with limitations of design or execution	• Consensus of expert opinion based on clinical experience

	• One or more RCTs corroborated by high-quality registry studies	• Meta-analyses of moderate-quality RCTs	observational studies, or registry studies • Meta-analyses of such studies	• Meta-analyses of such studies; or physiological or mechanistic studies in human subjects	
Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; RCT = randomized controlled trial					

European Society Of Cardiology Guidelines for the Management Of Elevated Blood Pressure and Hypertension (2024)

One of the most important changes in the ESC 2024 Guidelines is the focus on evidence related to CVD outcomes of BP-lowering interventions rather than BP lowering alone.[5] The major drug classes with robust evidence for BP-mediated reduction in CVD events are ACE inhibitors, ARBs, dihydropyridine CCBs, diuretics (thiazides and thiazide-like diuretics such as hydrochlorothiazide, chlorthalidone, and indapamide), and beta-blockers.[5] The first 4 medications are recommended as first-line options for starting hypertension treatment in the general population.[5] Beta-blockers can be added preferentially in circumstances such as in the presence of angina or heart failure, after myocardial infarction, or for controlling heart rate, where they are the cornerstone of therapy.[5] In such settings, second-generation (cardioselective) and, specifically, third-generation (vasodilating) beta-blockers are preferred.[5] However, beta-blockers are less effective than ACE inhibitors, ARBs, CCBs, or diuretics at preventing stroke, and have a higher discontinuation rate due to side effects.[5] Beta-blockers and diuretics, especially when combined, are associated with an increased risk of new-onset diabetes in predisposed patients.[5] The effect of RAS blockers and CCBs on preventing progression of hypertension-mediated organ damage also appears to be superior to beta-blockers.[5] Beta-blockers should also be avoided in patients with isolated systolic hypertension or more generally with arterial stiffness, as they increase stroke volume (given the lower heart rate).[5]

To treat hypertension, many patients will require more than one BP-lowering medication. Combining drugs from different drug classes can have additive or synergistic effects and lead to greater BP reduction than increasing the dose of one drug.[5] The superior BP-lowering efficacy of combination therapy is mediated, at least in part, by the potential of combination therapy to target multiple pathophysiological pathways contributing to perturbed BP in each patient.[5] A further benefit of combination therapy is the potential to use lower doses of each individual BP-lowering agent, which may reduce side effects and improve adherence and persistence, though the evidence for this hypothesis has been questioned.[5] Another caveat is that the evidence for reduced CVD outcomes with BP-lowering drugs in combination therapy is based on observational studies.[5] There are no outcomes data from prospective trials that prove superiority of upfront combination therapy (either as single-pill combinations or as separate pills) over upfront monotherapy in the isolated treatment of hypertension.[5] If combination BP-lowering therapy is pursued, single-pill combinations are preferred.[5]

The magnitude of BP reduction achieved with the main classes of BP-lowering medications (ACE inhibitors, ARBs, dihydropyridine CCBs, diuretics, and beta-blockers) as monotherapy is similar overall.[5] Blood pressure reduction with standard doses of any of these 5 classes can be expected to be approximately 9/5 mmHg with office BP and 5/3 mmHg with ambulatory BP monitoring.[5] These BP-lowering effects may attenuate over time.[5] Combination therapy (e.g. with 3 drugs at half standard dose) over the short term can lower office BP by up to 20/11 mmHg.[5] The pharmacologic recommendations for treating hypertension are presented in **Table 2**. The definitions for the recommendations and level of evidence used to guide the recommendations are summarized below.

Classes of Recommendations[5]

Class I: Evidence and/or general agreement that a given treatment is beneficial, useful, effective.
Class II: Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a given treatment.
Class IIa: Weight of evidence is in favor of usefulness/efficacy
Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
Class III: Evidence or general agreement that the given treatment is not useful/effective, and in some cases may be harmful.

Levels of Evidence[5]
A: Data derived from multiple RCTs or meta-analyses
B: Data derived from a single RCT or large non-randomized studies
C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Table 2. ESC Guidance for Pharmacological Treatment of Hypertension[5]

Recommendation	Class of Recommendation	Level of Evidence
Among all BP-lowering drugs, ACE inhibitors, ARBs, dihydropyridine CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated the most effective reduction of BP and CVD events, and are therefore recommended as first-line treatments to lower BP.	I	A
It is recommended that beta-blockers are combined with any of the other major BP-lowering classes when there are other compelling indications for their use, e.g., angina, post myocardial infarction, heart failure with reduced ejection fraction, or for heart rate control.	I	A
Given trial evidence for more effective BP control versus monotherapy, combination BP-lowering treatment is recommended for most patients with confirmed hypertension (BP> 140/90 mm Hg) as initial therapy. Preferred combinations are RAS blockers (either an ACEI or ARB) with a dihydropyridine CCB or diuretic. Exceptions to consider included patients aged ≥ 85 years, those with symptomatic orthostatic hypotension, moderate-to-severe frailty, or elevated BP (systolic BP 120-129 mm Hg or diastolic BP 70-89 mm Hg) with a concomitant indication for treatment.	I	B
In patients receiving combination BP-lowering treatment, fixed-dose single-pill combination treatment is recommended.	I	B
If BP is not controlled with a two-drug combination, increasing to a three-drug combination is recommended, usually a RAS blocker with a dihydropyridine CCB and thiazide/thiazide-like diuretic, and preferably in a single-pill combination.	I	B
If BP is not controlled with a three-drug combination, adding spironolactone should be considered.	IIa	B
If BP is not controlled with a three-drug combination and in whom spironolactone is not effective or tolerated, treatment with eplerenone instead of spironolactone, or the addition of a beta-blocker if not already indicated and, net a centrally acting BP medications, an alpha-blocker, hydralazine or potassium-sparing diuretic should be considered.	IIa	B
Combining two RAS blockers (ACEI and ARB) is not recommended.	III	A
Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CVD = cardiovascular disease; ESC = European Society of Cardiology; RAS = renin-angiotensin system		

Veterans Affairs/Department of Defense: Diagnosis and Management of Hypertension in Primary Care (2020)

This guideline updated hypertension recommendations that were published in 2014. The guideline working group, on the basis of their review of the literature, defined hypertension as an SBP of 130 mm Hg or greater or a DBP of 90 mm Hg or greater.[6] Evidence supports the use of a thiazide-type diuretic, a CCB, or either an ACE inhibitor or an ARB as primary pharmacologic therapy for hypertension.[6] The effects of the various antihypertensive drug classes on reducing composite CV outcomes, and not just differences in blood pressure–lowering effect, were the focus of the recommendation.[6] Although individual outcomes, such as heart failure or stroke, showed differences between classes, these individual differences were not significant when combined into the composite outcome, when age or ethnicity was not considered.[6] Therefore, for the overall reduction in CV outcomes, any of the antihypertensive drug therapies in the classes mentioned are reasonable first-, second-, or third-line therapy when data from all ages and ethnicities are considered together.[6]

Resistant hypertension (RHT) is defined as blood pressure not adequately controlled with a maximally tolerated dose of triple therapy (a thiazide-type diuretic, a CCB, and either an ACE inhibitor or an ARB).[6] Before adding a fourth drug to the treatment regimen, medication adherence should be assessed and the benefits of nonpharmacologic therapy should be reinforced in every patient who meets the criteria for RHT.[6] For patients with confirmed RHT, the addition of the MRA spironolactone is suggested for additional blood pressure reduction.[6] Drugs other than spironolactone may be more appropriate for patients with RHT who have a history of hyperkalemia, clinically significantly impaired kidney function, or sexual dysfunction or have developed either mastodynia or gynecomastia upon exposure to this drug in the past.[6] Specific goals of therapy and pharmacologic treatment recommendations are summarized in **Table 3**.

Table 3. Veterans Affairs/Department of Defense Recommendations for Hypertension Management[6]

Recommendation	Strength of the Recommendation
For all patients, including those with type 2 diabetes, we suggest treating them to a systolic blood pressure goal <130 mm Hg	Weak For
For patients 60 years and older, we recommend treating to a systolic blood pressure goal of < 150 mm Hg with added benefit to lowering systolic blood pressure further for those between 130 mm Hg and 150 mm Hg.	Strong For
For patients 60 years and older with type 2 diabetes, we recommend treating systolic blood pressure to a goal of < 140 mm Hg with added benefit to lowering systolic blood pressure further for those between 130 mm Hg and 140 mm Hg.	Strong For
For patients 30 years and over, we recommend treating to diastolic blood pressure goal of < 90 mm Hg.	Strong For
We recommend offering a thiazide-type diuretic, calcium channel blocker, or either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker as primary pharmacologic therapy for hypertension for reduction in composite cardiovascular outcomes.	Strong For
In African American patients with hypertension, we recommend against using an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker as monotherapy.	Strong Against
In hypertensive patients 65 years and over, we suggest a thiazide type diuretic for reduction in composite cardiovascular outcomes.	Weak For
We recommend against more than one of the following 3 drug classes together in the same patient: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors.	Strong Against
For the treatment of hypertension, there is insufficient evidence to recommend for or against initiating combination therapy over initiating monotherapy with the sequential addition of another medication	Neither For Nor Against
For patients with resistant hypertension (defined as those who are not adequately controlled with maximally tolerated dose of triple therapy [i.e., a thiazide-type diuretic, calcium channel blockers, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker]), we suggest adding spironolactone in those patients without contraindications.	Weak For

National Institute for Health and Care Excellence: Hypertension Management in Adults (2019)

NICE guidance for hypertension was updated in 2019, with additional updates in 2026.[7] All the guidance presented below is from 2019.

- Offer antihypertensive drug treatment in addition to lifestyle advice to adults of any age with persistent stage 2 hypertension (clinic BP of 160/100 mmHg or higher but less than 180/120 mmHg and subsequent ambulatory BP monitoring daytime average or home BP monitoring average blood pressure of 150/95 mmHg or higher).[7]
- Discuss starting antihypertensive drug treatment, in addition to lifestyle advice, with adults aged under 80 years with persistent stage 1 hypertension

(clinic BP ranging from 140/90 mm Hg to 159/99 mm Hg and subsequent ambulatory BP monitoring daytime average or home BP monitoring average ranging from 135/85 mm Hg to 149/94 mm Hg) who have 1 or more of the following: target organ damage, established CVD, renal disease, diabetes, or an estimated 10-year risk of CVD of 10% or more.[7]

- Offer an ARB or ACE inhibitor (titrate to the highest licensed dose that the person can tolerate) to adults, children, and young people with CKD and hypertension.[7]
- Offer an ACE inhibitor or ARB to adults starting step 1 antihypertensive treatment who have type 2 diabetes and are of any age or family origin or are aged under 55 years but not of Black African or African-Caribbean family origin.[7]
- When choosing antihypertensive drug treatment for adults of Black African or African-Caribbean family origin, consider an ARB in preference to an ACE inhibitor.[7]
- Do not combine an ACE inhibitor with an ARB to treat hypertension.[7]
- Offer a CCB to adults starting step 1 antihypertensive treatment who are aged 55 years and over and do not have type 2 diabetes or are of Black African or African-Caribbean family origin and do not have type 2 diabetes (of any age).[7]
- If a CCB is not tolerated, for example because of edema, offer a thiazide-like diuretic to treat hypertension.[7]
- If starting or changing diuretic treatment for hypertension, offer a thiazide-like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as HCTZ.[7]
- If hypertension is not controlled in adults taking step 1 treatment of an ACE inhibitor or ARB, offer a choice of a CCB or thiazide-like diuretic in addition to step 1 treatment.[7]
- If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or ARB plus CCB and a thiazide-like diuretic, regard them as having resistant hypertension. Consider adding an alpha-blocker or beta-blocker for adults with resistant hypertension who have a blood potassium level greater than 4.5 mmol/L.[7]
- Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with 1 of the following: labetalol (oral or intravenous), oral nifedipine, or intravenous hydralazine.[7]
- For secondary prevention, offer people who have had an MI treatment with an ACE inhibitor, dual platelet therapy (unless they have a separate indication for anticoagulation), beta-blocker and statin.[7]
- For people with HFrEF offer an ACE inhibitor, beta-blocker, MRA, and sodium glucose transporter-2 (SGLT2) inhibitor.[7]
- Offer either a beta-blocker or CCB as first-line treatment for stable angina. If the person cannot tolerate the beta-blocker or CCB, consider switching to the other option (CCB or beta-blocker).[7]
- First line therapy for hypertension in adults with type 1 diabetes is a RAS blocking drug.[7]

Additional Guidelines for Clinical Context:
After review, 5 guidelines were excluded due to poor quality.[21-25]

New Formulations:
12/2025: A new 10 mg/mL oral solution of LOPRESSOR (metoprolol) received FDA approval, indicated for the treatment of adults with hypertension, in the long-term treatment of angina pectoris, and the in the treatment of hemodynamically stable patients with definite or suspected MI, to reduce the risk of CV mortality when used in conjunction with intravenous metoprolol therapy.[8] The manufacturer did not conduct non-clinical and clinical studies for this new formulation and relied on the FDA's finding of safety and effectiveness metoprolol tablets.

7/2025: The FDA approved SDAMLO, new unit-dose oral solution formulation of amlodipine.[9] This product is supplied in 2.5 mg, 5 mg, and 10 mg unit of use bottles that each contain amlodipine powder that must be reconstituted prior to administration.[9] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[9] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications. The New Drug Application (NDA) was supported by a relative comparative bioavailability study of SDAMLO oral solution 5 mg and amlodipine 5 mg tablets.

6/2025: A new triple combination oral tablet, WIDAPLIK (telmisartan/amlodipine/indapamide) received FDA-approval, indicated for the treatment of hypertension in adults [10] The product is available in 3 strengths containing telmisartan/amlodipine, and indapamide in the following combinations: 10 mg/1.25 mg/0.625 mg; 20 mg/2.5 mg/1.25 mg; and 40 mg/5 mg/2.5 mg.[10] The efficacy of WIDAPLIK in lowering BP was evaluated in a randomized study designed to evaluate the efficacy and safety of two doses of WIDAPLIK (10 mg/1.25 mg/0.625 mg and 20 mg/2.5 mg/1.25 mg) compared to placebo (Study 1, NCT04518306) and in a randomized study designed to evaluate the efficacy and safety of WIDAPLIK (40 mg/5 mg/2.5 mg) as compared to each of its two-drug combinations at the same doses (Study 2, NCT04518293).[10]

In Study 1, the primary endpoint was the change from baseline to Week 4 in home SBP.[10] Both doses of WIDAPLIK showed statistically significant greater reductions in home SBP compared to placebo (see **Table 4).**

Table 4. Change From Baseline to Week 4 in Systolic Blood Pressure With Triple Therapy vs. Placebo in Study 1[10]

Systolic Blood Pressure (mm Hg)	**Placebo N=63**	**Telmisartan/Amlodipine/Indapamide 10 mg/1.25 mg/0.625 mg N=113**	**Telmisartan/Amlodipine/Indapamide 20 mg/2.25 mg/1.25 mg N=119**
Baseline, Mean	138.7	138.4	138.8
Week 4, Mean	136.4	129.2	128.0
LSM Change from Baseline	-2.2	-9.6	-10.4
LSM Difference Vs. Placebo		-7.3 (95% CI -10.2 to 0.45) P<0.001	-8.2 (95% CI -11.3 to -5.2) P<0.001
Abbreviations: CI = confidence interval; Hg = mercury; mg = milligrams; mm = millimeters; LSM = least-squares mean; N = number; NR = not reported			

In Study 2, the primary endpoint was the change in home seated mean SBP from baseline to Week 12.[10] WIDAPLIK (40 mg/5 mg/2.5 mg) showed statistically significant greater reductions in home SBP compared to each of the dual combinations (see **Table 5**).[10]

Table 5. Change From Baseline to Week 12 in Blood Pressure with Triple Therapy vs. Dual Therapy in Study 2[10]

Systolic Blood Pressure (mm Hg)	**Telmisartan/Amlodipine/Indapamide 10 mg/1.25 mg/0.625 mg N=551**	**Telmisartan/Indapamide 40 mg/2.5 mg N=276**	**Telmisartan/Amlodipine 40 mg/5 mg N=282**	**Amlodipine/Indapamide 5 mg/2.5 mg N=276**
Baseline, Mean	128.7	128.9	128.4	129.2

Week 4, Mean	124.0	126.5	129.4	128.8
LSM Change from Baseline	-4.0	-1.5	1.4	0.5
LSM Difference vs. Dual Comparator		-2.5 (95% CI -3.7 to -1.3) P<0.0001	-5.4 (95% CI -6.8 to -4.1) P<0.0001	-4.4 (-5.8 to -3.1) P<0.0001
Abbreviations: CI = confidence interval; Hg = mercury; mg = milligrams; mm = millimeters; LSM = least-squares mean; N = number				

There are no studies of WIDAPLIK demonstrating reductions in CV risk in patients with hypertension; however, previous studies with amlodipine, indapamide and several angiotensin II receptor blockers, which are in the same pharmacological class as the telmisartan component, have demonstrated such benefits.[10] Safety data were obtained from two placebo-controlled RCTS that included 1,680 patients with hypertension of whom 782 received WIDAPLIK.[10] Symptomatic hypotension, hyponatremia, and hypokalemia were more common with active treatment than placebo.[10] Most cases were mild to moderate in severity.[10]

2/2022: The FDA approved NORLIQVA, new 1 mg/mL oral solution formulation of amlodipine.[11] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[11] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications. No new clinical efficacy data was submitted to the FDA in the NDA.

12/2019: A new medication, CONJPRI, levamlodipine oral tablets were FDA-approved to treat hypertension in adults and pediatric patients aged 6 years an older either alone or in combination with other antihypertensive agents.[12] Levamlodipine is an active isomer of amlodipine.[12] The recommended adult starting dose is 2.5 mg orally once daily with a maximum dose of 5 mg once daily.[12] The recommended pediatric dose is 1.25 mg to 2.5 mg once daily.[12] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications. No new clinical efficacy data was submitted to the FDA in the NDA. Levamlodipine has been approved and marketed in China since 2003.[12] There is no evidence that levamlodipine is more effective than amlodipine.

7/2019: The FDA approved KATERZIA, new 1 mg/mL oral solution formulation of amlodipine.[13] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[13] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications. No new clinical efficacy data was submitted to the FDA in the NDA.

6/2016: The FDA approved an oral tablet combination product, BYVALSON (nebivolol/valsartan 5mg/80mg), indicated for the treatment of hypertension.[14] BYVALSON was studied in a Phase 3, double-blind, placebo-controlled, dose-escalating, 8-week study in 4,161 patients with Stage 1 or 2 hypertension.[14] Patients were initially randomized to 1 of 8 treatment groups including: 3 fixed-dose combinations of nebivolol and valsartan (5 mg/ 80 mg, 5 mg/ 160 mg, 10 mg/ 160 mg), nebivolol monotherapy (5 mg, 20 mg), valsartan monotherapy (80 mg, 160 mg), or placebo. After 4 weeks of treatment, all doses were doubled in the fixed-dose combination. groups (to 10 mg/ 160 mg, 10 mg/ 320 mg, and 20 mg/ 320 mg), nebivolol monotherapy groups (to 10 mg, 40 mg), and valsartan monotherapy groups (to 160 mg, 320 mg).[14] Treatment with BYVALSON 5 mg/ 80 mg for 4 weeks resulted in placebo-adjusted reductions from baseline in SBP and DBP of -8.3 and -7.2 mmHg, respectively.[14] Treatment with BYVALSON 5 mg/ 80 mg resulted in greater reductions in SBP and DBP than did treatment with nebivolol 5 mg alone ($p<0.0001$ for both SBP and DBP) or valsartan 80 mg, alone ($p=0.0007$ for SBP and $p<0.0001$ for DBP).[14]

The safety of the 5 mg/ 80 mg dose of nebivolol/valsartan was evaluated during the first 4 weeks of the 8-week placebo-controlled trial. During the 4-week period, the overall incidence of adverse events on therapy with BYVALSON 5 mg/ 80 mg was similar to placebo and the individual components (nebivolol 5 mg and valsartan 80 mg).[14] Discontinuation of therapy due to a clinical adverse event occurred in 2.0% of patients treated with BYVALSON 5 mg/ 80 mg versus 3.2% of patients given placebo and approximately 1% of patients given nebivolol 5 mg or valsartan 80 mg as monotherapy.[14]

New FDA Safety Alerts:

Table 6. Description of New FDA Safety Alerts[26]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Metoprolol	KAPSPARGO LOPRESSOR TOPROL XL	4/2023	Warnings and Precautions	**Anaphylactic Reaction** While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction. **Bradycardia** Bradycardia, including sinus pause, heart block, and cardiac arrest have occurred with the use of metoprolol succinate. Patients with first-degree atrioventricular block, sinus node dysfunction, conduction disorders (including Wolff-Parkinson-White) or on concomitant drugs that cause bradycardia, may be at increased risk. Monitor heart rate in patients receiving metoprolol succinate. If severe bradycardia develops, reduce or stop metoprolol succinate. **Hypoglycemia** Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at any time during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.
Esmolol	BREVIBLOC	5/2024	Warnings and Precautions	**Hypoglycemia** Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at any time during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.

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9. SMDAMLO (amlodipine) for oral solution. Prescribing Information. Edison, NJ; Brillian Pharma Inc. 7/2025.
10. WIDAPLIK (telmisartan, amlodipine, and indapamide) oral tablets. Prescribing Information. Pradesh, India; Piramal Pharma Limited. 6/2025.
11. NORLIQVA (amlodipine) oral solution. Prescribing Information. Farmville, NC; CMP Pharma, Inc. 2/2022.
12. CONJUPRI (levamlodipine) oral tablets. Prescribing Information. Hebei Province, China; CSPC Ouyi Pharmaceutical Co., Ltd. 12/2019.
13. KATERZIA (amlodipine) oral suspension. Prescribing Information. Greenwood Village, CO; Silvergate Pharmaceuticals, Inc. 7/2019.
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Appendix 1: Current Preferred Drug List

Combination Antihypertensives

Generic	Brand	Form	PDL
amlodipine bes/olmesartan med	AMLODIPINE-OLMESARTAN	TABLET	Y
amlodipine bes/olmesartan med	AZOR	TABLET	Y
benazepril/hydrochlorothiazide	BENAZEPRIL-HYDROCHLOROTHIAZIDE	TABLET	Y
benazepril/hydrochlorothiazide	LOTENSIN HCT	TABLET	Y
enalapril/hydrochlorothiazide	ENALAPRIL MALEATE/HCTZ	TABLET	Y
enalapril/hydrochlorothiazide	ENALAPRIL-HYDROCHLOROTHIAZIDE	TABLET	Y
lisinopril/hydrochlorothiazide	LISINOPRIL-HYDROCHLOROTHIAZIDE	TABLET	Y
lisinopril/hydrochlorothiazide	ZESTORETIC	TABLET	Y
losartan/hydrochlorothiazide	HYZAAR	TABLET	Y
losartan/hydrochlorothiazide	LOSARTAN-HYDROCHLOROTHIAZIDE	TABLET	Y
olmesartan/amlodipin/hcthiazid	OLMESARTAN-AMLODIPINE-HCTZ	TABLET	Y
olmesartan/amlodipin/hcthiazid	TRIBENZOR	TABLET	Y
olmesartan/hydrochlorothiazide	BENICAR HCT	TABLET	Y
olmesartan/hydrochlorothiazide	OLMESARTAN-HYDROCHLOROTHIAZIDE	TABLET	Y
telmisartan/hydrochlorothiazid	MICARDIS HCT	TABLET	Y
telmisartan/hydrochlorothiazid	TELMISARTAN-HYDROCHLOROTHIAZID	TABLET	Y
amlodipine besylate/benazepril	AMLODIPINE BESYLATE-BENAZEPRIL	CAPSULE	N
amlodipine besylate/benazepril	LOTREL	CAPSULE	N
amlodipine besylate/valsartan	AMLODIPINE-VALSARTAN	TABLET	N
amlodipine besylate/valsartan	EXFORGE	TABLET	N
amlodipine/atorvastatin	AMLODIPINE-ATORVASTATIN	TABLET	N
amlodipine/atorvastatin	CADUET	TABLET	N
amlodipine/valsartan/hcthiazid	AMLODIPINE-VALSARTAN-HCTZ	TABLET	N
atenolol/chlorthalidone	ATENOLOL W/CHLORTHALIDONE	TABLET	N
atenolol/chlorthalidone	ATENOLOL-CHLORTHALIDONE	TABLET	N
atenolol/chlorthalidone	TENORETIC 100	TABLET	N
atenolol/chlorthalidone	TENORETIC 50	TABLET	N
azilsartan med/chlorthalidone	EDARBYCLOR	TABLET	N
bisoprolol/hydrochlorothiazide	BISOPROLOL FUMARATE/HCTZ	TABLET	N
bisoprolol/hydrochlorothiazide	BISOPROLOL-HYDROCHLOROTHIAZIDE	TABLET	N
candesartan/hydrochlorothiazid	ATACAND HCT	TABLET	N
candesartan/hydrochlorothiazid	CANDESARTAN-HYDROCHLOROTHIAZID	TABLET	N
captopril/hydrochlorothiazide	CAPTOPRIL/HYDROCHLOROTHIAZIDE	TABLET	N
captopril/hydrochlorothiazide	CAPTOPRIL-HYDROCHLOROTHIAZIDE	TABLET	N
fosinopril/hydrochlorothiazide	FOSINOPRIL-HYDROCHLOROTHIAZIDE	TABLET	N
irbesartan/hydrochlorothiazide	AVALIDE	TABLET	N
irbesartan/hydrochlorothiazide	IRBESARTAN-HYDROCHLOROTHIAZIDE	TABLET	N

metoprolol/hydrochlorothiazide	METOPROLOL-HYDROCHLOROTHIAZIDE	TABLET	N
propranolol/hydrochlorothiazid	PROPRANOLOL HCL W/HCTZ	TABLET	N
quinapril/hydrochlorothiazide	ACCURETIC	TABLET	N
quinapril/hydrochlorothiazide	QUINAPRIL-HYDROCHLOROTHIAZIDE	TABLET	N
telmisartan/amlodipine	TELMISARTAN-AMLODIPINE	TABLET	N
trandolapril/verapamil HCl	TRANDOLAPRIL-VERAPAMIL ER	TAB BP 24H	N
valsartan/hydrochlorothiazide	DIOVAN HCT	TABLET	N
valsartan/hydrochlorothiazide	VALSARTAN-HYDROCHLOROTHIAZIDE	TABLET	N
telmisartan/amlodipine/indapam	WIDAPLIK	TABLET	

Calcium Channel Blockers – Dihydropyridine, Oral

Generic	Brand	Form	PDL
amlodipine besylate	AMLODIPINE BESYLATE	TABLET	Y
amlodipine besylate	NORVASC	TABLET	Y
nicardipine HCl	NICARDIPINE HCL	CAPSULE	Y
nifedipine	NIFEDIPINE ER	TAB ER 24	Y
nifedipine	PROCARDIA XL	TAB ER 24	Y
nifedipine	NIFEDIPINE ER	TABLET ER	Y
amlodipine benzoate	KATERZIA	ORAL SUSP	N
amlodipine besylate	SDAMLO	POWDER CON	N
amlodipine besylate	NORLIQVA	SOLUTION	N
felodipine	FELODIPINE ER	TAB ER 24H	N
isradipine	ISRADIPINE	CAPSULE	N
levamlodipine maleate	LEVAMLODIPINE MALEATE	TABLET	N
nifedipine	NIFEDIPINE	CAPSULE	N
nisoldipine	NISOLDIPINE	TAB ER 24H	N
nisoldipine	SULAR	TAB ER 24H	N
nimodipine	NIMODIPINE	CAPSULE	
nimodipine	NIMOTOP	CAPSULE	
nimodipine	NIMODIPINE	SOLUTION	
nimodipine	NYMALIZE	SOLUTION	N
nimodipine	NYMALIZE	SYRINGE	N

Calcium Channel Blockers – Non-dihydropyridine, Oral

Generic	Brand	Form	PDL
diltiazem HCl	CARDIZEM SR	CAP ER 12H	Y
diltiazem HCl	DILTIAZEM 12HR ER	CAP ER 12H	Y
diltiazem HCl	DILTIAZEM 12HR ER	CAP ER 12H	Y
diltiazem HCl	DILTIAZEM HCL	CAP ER 12H	Y
diltiazem HCl	DILTIAZEM HCL	CAP ER 12H	Y

diltiazem HCl	CARDIZEM CD	CAP ER 24H	Y
diltiazem HCl	CARTIA XT	CAP ER 24H	Y
diltiazem HCl	CARTIA XT	CAP ER 24H	Y
diltiazem HCl	DILTIAZEM 24HR ER	CAP ER 24H	Y
diltiazem HCl	DILTIAZEM 24HR ER (CD)	CAP ER 24H	Y
diltiazem HCl	DILTIAZEM 24HR ER (CD)	CAP ER 24H	Y
diltiazem HCl	DILTIAZEM HCL	CAP ER 24H	Y
diltiazem HCl	DILACOR XR	CAP ER DEG	Y
diltiazem HCl	DILTIAZEM 24HR ER (XR)	CAP ER DEG	Y
diltiazem HCl	DILTIAZEM 24HR ER (XR)	CAP ER DEG	Y
diltiazem HCl	DILT-XR	CAP ER DEG	Y
diltiazem HCl	DILTIAZEM 24HR ER	CAP SA 24H	Y
diltiazem HCl	DILTIAZEM 24HR ER	CAP SA 24H	Y
diltiazem HCl	TIADYLT ER	CAP SA 24H	Y
diltiazem HCl	TIAZAC	CAP SA 24H	Y
diltiazem HCl	CARDIZEM	TABLET	Y
diltiazem HCl	DILTIAZEM HCL	TABLET	Y
diltiazem HCl	DILTIAZEM HCL	TABLET	Y
verapamil HCl	VERAPAMIL ER	CAP24H PEL	Y
verapamil HCl	VERAPAMIL HCL	CAP24H PEL	Y
verapamil HCl	VERAPAMIL SR	CAP24H PEL	Y
verapamil HCl	VERAPAMIL SR	CAP24H PEL	Y
verapamil HCl	VERAPAMIL HCL	TABLET	Y
verapamil HCl	VERAPAMIL HCL	TABLET	Y
verapamil HCl	CALAN SR	TABLET ER	Y
verapamil HCl	ISOPTIN S.R.	TABLET ER	Y
verapamil HCl	VERAPAMIL ER	TABLET ER	Y
verapamil HCl	VERAPAMIL ER	TABLET ER	Y
diltiazem HCl	CARDIZEM LA	TAB ER 24H	N
diltiazem HCl	DILTIAZEM 24HR ER (LA)	TAB ER 24H	N
diltiazem HCl	DILTIAZEM 24HR ER (LA)	TAB ER 24H	N
diltiazem HCl	MATZIM LA	TAB ER 24H	N
verapamil HCl	VERAPAMIL ER PM	CAP24H PCT	N
verapamil HCl	VERELAN PM	CAP24H PCT	N

Beta-blockers, oral

Generic	Brand	Form	PDL
acebutolol HCl	ACEBUTOLOL HCL	CAPSULE	Y
atenolol	ATENOLOL	TABLET	Y
atenolol	TENORMIN	TABLET	Y

carvedilol	CARVEDILOL	TABLET	Y
labetalol HCl	LABETALOL HCL	TABLET	Y
metoprolol succinate	METOPROLOL SUCCINATE	TAB ER 24H	Y
metoprolol succinate	TOPROL XL	TAB ER 24H	Y
metoprolol tartrate	LOPRESSOR	TABLET	Y
metoprolol tartrate	METOPROLOL TARTRATE	TABLET	Y
nadolol	NADOLOL	TABLET	Y
propranolol HCl	INDERAL LA	CAP SA 24H	Y
propranolol HCl	PROPRANOLOL HCL ER	CAP SA 24H	Y
propranolol HCl	PROPRANOLOL HCL	SOLUTION	Y
propranolol HCl	PROPRANOLOL HCL	TABLET	Y
betaxolol HCl	BETAXOLOL HCL	TABLET	N
bisoprolol fumarate	BISOPROLOL FUMARATE	TABLET	N
carvedilol phosphate	CARVEDILOL ER	CPMP 24HR	N
labetalol HCl	LABETALOL HCL	TABLET	N
metoprolol succinate	KAPSPARGO SPRINKLE	CAP SPR 24	N
metoprolol tartrate	LOPRESSOR	SOLUTION	N
metoprolol tartrate	METOPROLOL TARTRATE	TABLET	N
nebivolol HCl	BYSTOLIC	TABLET	N
nebivolol HCl	NEBIVOLOL HCL	TABLET	N
pindolol	PINDOLOL	TABLET	N
propranolol HCl	INDERAL XL	CAP ER 24H	N
propranolol HCl	INNOPRAN XL	CAP ER 24H	N
propranolol HCl	HEMANGEOL	SOLUTION	N
sotalol HCl	SOTYLIZE	SOLUTION	N
sotalol HCl	BETAPACE	TABLET	N
sotalol HCl	BETAPACE AF	TABLET	N
sotalol HCl	SOTALOL	TABLET	N
sotalol HCl	SOTALOL AF	TABLET	N
timolol maleate	BLOCADREN	TABLET	N
timolol maleate	TIMOLOL MALEATE	TABLET	N
propranolol HCl	HEMANGEOL	SOLUTION	N

Appendix 2: New Comparative Clinical Trials

A total of 110 citations were manually reviewed from the initial literature search. After further review, 110 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Beta Blockers
Ovid MEDLINE(R) ALL <1946 to May 15, 2026>

1	exp Acebutolol/	862
2	exp Atenolol/	5401
3	exp Carvedilol/	3059
4	exp Labetalol/	1969
5	exp Metoprolol/	5882
6	exp Betaxolol/	688
7	exp Bisoprolol/	1299
8	exp Nadolol/	839
9	exp Nebivolol/	919
10	exp Pindolol/	3719
11	exp Propranolol/	33401
12	exp Sotalol/	2184
13	Timolol/	3994
14	exp Administration, Oral/	167345
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	57850
16	14 and 15	2017
17	limit 16 to (english language and humans and yr="2022 -Current")	72

Calcium Channel Blockers
Ovid MEDLINE(R) ALL <1946 to May 15, 2026>

1	Calcium Channel Blockers/ or Amlodipine, Valsartan Drug Combination/ or Amlodipine Besylate, Olmesartan Medoxomil Drug Combination/ or Amlodipine/	40961
2	Nicardipine/	2624
3	Nifedipine/	16035
4	Felodipine/	1298
5	Isradipine/	1379
6	levamlodipine.mp.	33
7	nisodipine.mp.	3
8	Nimodipine/	2971
9	Diltiazem/	6384
10	Verapamil/	17149

11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	69584
12	Administration, Oral/	163357
13	11 and 12	1870
14	limit 13 to (english language and humans)	1264
15	limit 14 to yr="2015 -Current"	196
16	limit 15 to (comparative study or guideline or meta-analysis or practice guideline or "systematic review")	38

Appendix 4: Key Inclusion Criteria

Population	**Adults with hypertension**
Intervention	Beta-blockers and calcium channel blockers in Appendix 1
Comparator	Beta-blockers and calcium channel blockers in Appendix 1, diuretics, angiotensin converting enzyme inhibitors and angiotensin receptor blockers
Outcomes	Reductions in blood pressure
Timing	4- 8 weeks
Setting	Outpatient