NOVEL AND EMERGING PHARMACOTHERAPIES FOR TREATING HYPERTENSION

AANP CLINICAL RESOURCE TOOL

The Scope of the Problem

Hypertension (HTN) prevalence is expanding in the U.S., with nearly 50% of all American adults now living with HTN. Even worse, nearly 60% don't know it.

FOUNDATIONAL PRACTICE GAP:

Only 20.7% of American adults with HTN have blood pressure (BP) controlled below 130/80 mmHg. That means more than 100 million Americans are living with uncontrolled HTN.

HTN Treatment by the Numbers

- Only **51.2%** of American adults living with HTN receive pharmacotherapy of any kind.
- Over **50%** of American adults living with HTN taking 1 or 2 antihypertensives still do not achieve a BP <130/80 mmHg.
- Approximately **15-20%** of American adults living with HTN do not achieve BP <130/80 mmHg on ≥3 antihypertensives or require ≥4 antihypertensives to reach goal.

HTN CLINICAL PEARL:

HTN is formally classified as "resistant" if a patient is taking 3 or more antihypertensives and is still not at BP goal, OR if they require 4 or more antihypertensives to reach goal.

Resistant HTN Risk Factors

- Older age (>60 years).
- Obesity.
- Chronic kidney disease.
- Type 2 diabetes.
- Social determinants of health (e.g., living in health care professional shortage areas, socioeconomic disadvantages, racial/ethnic inequities).

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Did You Know? The more resistant the HTN, the more likely there is a secondary cause.

Common Causes of Secondary HTN	Uncommon Causes of Secondary HTN
• Primary aldosteronism. • Obstructive sleep apnea. • Chronic kidney disease. • Renovascular hypertension. • Drug or alcohol-induced.	• Hypo/hyperthyroidism. • Pheochromocytoma. • Cushing syndrome. • Aortic coarctation. • Congenital adrenal hyperplasia. • Acromegaly.

Far from Benign: The Clinical Ramifications of HTN

HTN, and especially HTN that remains uncontrolled for long periods of time, is associated with numerous risks across organ systems — including the heart, kidneys, eyes and brain, among others.

Did You Know? HTN is the leading modifiable risk factor for premature death.

Informing HTN Treatment Using Cardiovascular Risk Stratification

The 2025 ACC/AHA/Multi-Society BP Guideline now recommends using the Predicting Risk of Cardiovascular Disease EVENTs (PREVENT) equations to assess a patient's 10-year cardiovascular disease (CVD) risk. That value can then be used, in conjunction with other patient-specific factors, to determine BP thresholds and goals of treatment.

HTN CLINICAL PEARL:

The PREVENT Equations are NOT designed or intended for use in patients with existing clinical CVD. Instead, they should be used to determine total CVD risk in patients without existing CVD.

Many clinicians will be familiar with the Pooled Cohort Equations (PCEs), which were endorsed by prior ACC/AHA guidelines for assessment of atherosclerotic cardiovascular disease (ASCVD) risk. However, the PREVENT equations and the PCEs are not interchangeable — in fact, they have a host of important and practical differences.

PCE	PREVENT Equations
• Focuses on hard ASCVD clinical events (e.g., myocardial infarction and stroke). • Designed for ages 40-79 years. • Includes race as a risk variable. • Offers 10-year risk level assessment.	• Allows for global CVD risk assessment, including heart failure. • Designed for ages 30-79 years. • Removes race as a risk variable. • Added sex-specific variables. • Offers 10-year and 30-year risk level assessment. • Includes statin use as a predictor. • Incorporates renal function. • Has a "Full" option that includes A1c, uACR, and social deprivation index (SDI).

Bottom Line

- **PREVENT** achieved more accurate and comprehensive 10-year absolute CVD risk assessment than PCE, especially in men and non-Hispanic Black adults.

Did You Know?

Guideline-directed BP goals and treatment recommendations are based largely on 10-year CVD risk strata and/or the presence of existing CVD.

2025 ACC/AHA/MULTI-SOCIETY BP GUIDELINE RECOMMENDATIONS

RECOMMENDED BP GOALS BASED ON RISK

In adults with HTN with CVD risk ≥7.5%, SBP goal <130 mmHg (with encouragement to achieve <120 mmHg) to reduce CV events and mortality.

In adults with HTN with CVD risk <7.5%, SBP goal <130 mmHg (with encouragement to achieve <120 mmHg) may be reasonable to reduce risk of further BP elevation.

In adults with HTN with CVD risk ≥7.5%, DBP goal <80 mmHg is recommended to reduce the risk of CV events and mortality.

In adults with HTN with CVD risk <7.5%, DBP goal <80 mmHg may be reasonable to reduce risk of cardiovascular events

GUIDING HTN TREATMENT USING CVD RISK ESTIMATION

In all adults with HTN, initiate BP-lowering meds when average SBP ≥140 mmHg to reduce mortality and CV events.

In adults with HTN and clinical CVD, initiate BP-lowering meds when average DBP ≥80 mmHg to reduce mortality and CV events.

In adults with HTN and T2D or CKD or 10-year risk ≥7.5%, initiate BP-lowering meds when average SBP ≥130 mmHg to reduce mortality and CV events.

In adults with HTN and T2D or CKD or 10-year risk ≥7.5%, initiate BP-lowering meds when average DBP ≥80 mmHg to reduce mortality and CV events.

In adults with HTN and 10-year CVD risk <7.5%, initiate BP-lowering meds if average SBP remains ≥130 mmHg after 3-6-month trial of lifestyle change.

In adults with HTN and 10-year CVD risk <7.5%, initiate BP-lowering meds if average DBP remains ≥80 mmHg after 3-6-month trial of lifestyle change.

Preferred First-Line Pharmacologic Classes

- Thiazide-type diuretic.
- Long-acting dihydropyridine calcium channel blocker.
- Angiotensin-converting enzyme inhibitors.
- Angiotensin receptor blocker.

Did You Know?

Approximately 50% of patients will become nonadherent to their antihypertensive medications within 12 months of treatment initiation.

Guideline-Directed Management of Resistant HTN

The 2025 ACC/AHA/Multi-Society BP Guideline offers an evidence-based algorithm for managing resistant HTN. After confirming the diagnosis, excluding pseudoresistance, identifying and reversing contributing factors, discontinuing or minimizing interfering substances and screening for secondary causes, the Guideline recommends a stepwise approach to pharmacologic treatment:

Pharmacological Treatment

- Maximize diuretic therapy (replace thiazides with chlorthalidone or indapamide)
- Add spironolactone 25-30mg daily or equivalent dose of eplerenone if eGFR ≥45
- Use chlorthalidone or loop diuretics in patients with CKD stage 4 or greater
- Add agents with a different mechanism of action (i.e., beta blockers, central sympatholytics, or non-DHP CCBs)
- Add potent vasodilators (i.e.,aprocitentan, hydralazine, or minoxidil) if already on beta blocker and loop diuretic

- Maximize diuretic therapy (replace thiazides with chlorthalidone or indapamide).
- Add spironolactone 25-50 mg daily or equivalent dose of eplerenone if eGFR ≥45.
- Use chlorthalidone or loop diuretics in patients with chronic kidney disease stage 4 or greater.
- Add agents with a different mechanism of action (i.e., beta blockers, central sympatholytics, or non-dihydropyridine calcium channel blockers).
- Add potent vasodilators (i.e., aprocitentan, hydralazine, or minoxidil) if already on beta blocker and loop diuretic.

HTN CLINICAL PEARL:

Resistant HTN can be managed in the primary care setting, but specialist referral is recommended for known or suspected secondary HTN or if BP remains uncontrolled after 6 months on treatment.

At the Interface of HTN Pathophysiology and Novel Pharmacology

Advances in understanding of the pathophysiologic mechanisms underpinning HTN have led to a much-needed drug development renaissance, with the first novel mechanisms of action now entering the armamentarium in decades.

Aiming at the Renin-Angiotensin-Aldosterone System (RAAS) Cascade

- Aldosterone synthase inhibition.
  - Inhibit the production of aldosterone in the adrenal gland.

Did You Know? **The aldosterone synthase inhibitor (ASi), baxdrostat, has a pending PDUFA date with the FDA, seeking to become the first-in-class ASi to be approved for HTN.**

- Non-steroidal mineralocorticoid receptor antagonism.
  - Block aldosterone binding with the mineralocorticoid receptor, thus inhibiting aldosterone's key function in causing HTN — the retention of sodium and water.
- Hepatic angiotensinogen silencers.
  - siRNAs and ASOs both reduce the production of angiotensinogen in the liver, thereby downregulating the entire RAAS cascade by suppressing it upstream.

Aiming at Endothelin, a Potent Vasoconstrictor

- Dual endothelin receptor antagonism.
  - When ETA and ETB receptors are blocked, endothelin-1 is not able to bind, thus inhibiting its potent vasoconstricting effects at the level of vascular smooth muscle.

Did You Know? **The dual endothelin receptor antagonist, aprocitentan, became the first new antihypertensive medication in decades — and the first novel mechanism of action approved for HTN —when it achieved FDA approval in March 2024.**

HTN CLINICAL PEARL:

Primary care nurse practitioners (NPs) have an invaluable opportunity to individualize HTN treatment and promote health equity in HTN care by using active communication methods at the patient interface, principally shared decision-making and motivational interviewing.

Guidelines and Key References for NPs

2025 ACC/AHA/Multi-Society Blood Pressure Guideline:
https://www.ahajournals.org/doi/10.1161/CIR.0000000000001356

Access to Current FDA Product Labels:
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Access to Ongoing Clinical Trials of Novel HTN Therapies:
https://clinicaltrials.gov/

AANP Podcasts Focused on the Evolving Best Practice Management of HTN for NPs:
https://aanp.podbean.com/e/160-breaking-down-the-latest-hypertension-guidelines/
https://aanp.podbean.com/e/89-resistant-hypertension/