Circulation

ON MY MIND

# Mission "UnACCOMPLISHed"

## Optimal Antihypertensive Therapy

Robert D. Brook, MD
Phillip D. Levy, MD, MPH
Kenneth A. Jamerson, MD

In 2017, the American Heart Association/American College of Cardiology Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults made many new recommendations for the management of hypertension.[1] One key feature was an emphasis on using combination drug therapy, even for milder hypertension (stage 2; ≥140/90 mm Hg). This is especially pertinent given the promulgation of lower blood pressure (BP) goals <130/80 mm Hg, considering that most patients (>75%) require ≥2 medications to reach less stringent targets.[1] Other advantages of combination therapy include a greater and more uniform reduction in BP across differing patients (eg, race) than monotherapy. BP control is reached more rapidly with fewer medication changes and side effects. Single-pill combination medications (also reduce pill burden and improve compliance. Last, initial combination therapy may even reduce cardiovascular events compared with stepped-care approaches.[1]

Apart from stating "2 first-line agents from different classes" should be combined, the guidelines did not recommend any specific regimen.[1] A diuretic combined with a calcium channel blocker (CCB), or either drug class added to an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker, was deemed acceptable. This equipoise leads clinicians to surmise there is no evidence supporting the superiority of any combination over another. We disagree with this narrative and believe there is evidence to support preferred combinations.[2,3] One major outcome trial coupled with a host of other benefits and experimental findings support our opinion that CCB/ACEI should be the preferred first-line combination (Table).[2,3] By endorsing other combinations, guidelines may be failing to promote an optimized strategy to reduce the burden of cardio-renal disease.

We believe the compelling series of findings from the ACCOMPLISH trial (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) have been inappropriately disregarded by guidelines.[1–5] The principal results showed that treatment combining amlodipine, rather than hydrochlorothiazide, with benazepril reduced the primary composite end point (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac death, and coronary revascularization) by 20% (hazard ratio, 0.80 [95% CI, 0.72–0.90]; $P<0.001$) in 11 506 hypertensive adults.[2] Further analyses demonstrated that favorable cardiovascular outcomes extended to patients with diabetes, coronary heart disease, and chronic kidney disease, while also yielding superior nephroprotection.[3] Recent analyses showed the benefits occurred regardless of previous medication regimens (antihypertensive drugs, statins) and BP control.[4] Even patients who achieved a systolic BP <130 mm Hg (n=5221 [45.4%]; adjusted hazard ratio, 0.83 [95% CI, 0.70–0.99]) as well as those with apparent resistant hypertension taking ≥4 medications (n=4451 [38.7%]; hazard ratio, 0.81 [95% CI, 0.70–0.95]) benefited from starting with





Key Words: calcium channel blockers ■ diuretics ■ hypertension



https://www.ahajournals.org/journal/circ



*Circulation.* 2021;143:1932–1934. DOI: 10.1161/CIRCULATIONAHA.120.053151

**Table. Potential Benefits of Combining Amlodipine Versus a Diuretic With Renin-Angiotensin System Blockade**

| |
|---|
| Electrolytes and fluids |
| No decrease in serum sodium, potassium, or magnesium |
| No increase in serum calcium or uric acid |
| No potential dehydration or azotemia |
| Metabolic |
| No worsening of LDL-C |
| No increase in diabetes risk, worsening of glycemia or insulin resistance |
| Inflammation |
| Neutral effect on C-reactive protein vs slight worsening on diuretic |
| Plausible direct antioxidant and anti-inflammatory effects of amlodipine |
| Vascular/atherosclerosis |
| Improved endothelial-dependent vasodilation and nitric oxide bioavailability |
| Reduction in pulse-wave velocity and large vessel stiffness |
| Better mitigation of carotid intima-media thickness progression |
| Hemodynamics |
| Greater reduction in central aortic blood pressure and augmentation index when used alone and when combined with a renin-angiotensin system blocker |
| Lower short- and long-term blood pressure variability |
| Clinical effects |
| Better long-term compliance with amlodipine versus diuretics |
| Fewer total side effects |
| No need to monitor follow-up blood laboratory results |
| Potential adverse effects of amlodipine versus a diuretic |
| Lower extremity edema; however, this is mitigated when the dose is ≤5 mg per day and when combined with a renin-angiotensin system blocker |
| Potential for worse heart failure outcomes; however, this is mitigated when combined with a renin-angiotensin system blocker; Heart failure outcomes were not worse in ACCOMPLISH |
| Less reduction in albuminuria compared with a diuretic; however, in ACCOMPLISH, the composite renal outcomes favored CCB/ACEI combination |

The relevance of these factors for reducing hard cardiovascular events and explaining the results of ACCOMPLISH is unknown. However, because 24-hour blood pressure levels did not differ between treatment limbs, it is logical to posit that 1 or more of the listed "BP-independent" actions played a role. Detailed discussion and referencing of the experiments demonstrating these benefits can be found elsewhere.[3] ACCOMPLISH indicates Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension trial; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; and LDL-C, low-density lipoprotein cholesterol.

a CCB/ACEI combination.[5] This superior cardiovascular protection was "BP-independent" (ie, not caused by lower 24-hour ambulatory BP levels).[3] Although the underlying explanations remain to be fully elucidated, viable possibilities have been illustrated (Table).[3]

A common objection to our opinion is that if a thiazide-like diuretic (eg, chlorthalidone) replaced hydrochlorothiazide in ACCOMPLISH, there might have been no outcome differences. Thiazide-like diuretics are structurally different from thiazides, and despite similar renal actions, they are more potent, are longer-acting, and have superior trial evidence.[1] However, chlorthalidone would likely have led to a mismatched lower BP in its treatment limb, thereby obfuscating the capacity to examine for direct pharmacological benefit of either regimen. Because 24-hour BPs were reduced to nearly identical levels in both limbs, ACCOMPLISH was successful in providing compelling evidence for superior "BP-independent" cardioprotection from combining a CCB rather than a diuretic with an ACEI. Therefore, the only viable argument that a chlorthalidone-based regimen might prove equally protective at the same BP level must invoke speculative pleiotropic drug properties of thiazide-like diuretics (eg, carbonic anhydrase inhibition) of unproven clinical relevance. However unlikely this conjecture remains, what should be of preeminent importance when forming evidence-based guidelines is that the only trial that directly compared 2 combination antihypertensive regimens conclusively showed the superiority of CCB/ACEI.[2] Meta-analyses cannot be properly used to settle this issue as all other trials were designed to compare outcomes between groups assigned to different initial single agents.[1] The protocols for adding medications resulted in heterogeneous, biased, and often suboptimal combinations in some limbs. We contend that recommendations for using other combinations on equal footing lack (or overlook) the top-tier outcome trial evidence unique to CCB/ACEI.

From a real-world perspective, all single-pill combination medications between ACEIs (or angiotensin receptor blockers) and diuretics use hydrochlorothiazide, except for azilsartan/chlorthalidone. Even if or when a less expensive generic formulation becomes widely available, its usage cannot be implicitly favored over generic amlodipine/benazepril because it has not proven equal in an outcome trial. In the meantime, using a generic ACEI (or angiotensin receptor blocker) plus chlorthalidone requires 2 separate pills and undermines the benefits of single-pill combination medications.[1] Arguments have also been made that Black patients often need diuretics for hypertension control. However, BPs did not differ between treatments in the 1416 self-described Black participants in ACCOMPLISH.[2] Although CCBs have been linked to excess heart failure, this was not true when combined with an ACEI in ACCOMPLISH.[2] Last, some have argued that ACCOMPLISH is only 1 study and requires replication. However, many guideline recommendations have been adopted despite lower supporting levels of evidence than data from ACCOMPLISH—a large, high-quality outcome trial stopped early because of efficacy and $P<0.001$ for the primary end point.[2] Given the importance of resolving this issue, we believe an outcome trial is warranted to compare an ACEI (or angiotensin receptor blocker) combined with amlodipine versus chlorthalidone as first-line therapy in hypertensive patients receiving contemporary medical care.

There is uniform consensus that the majority of patients will require ≥2 medications to reach BP goals <130/80 mm Hg.[1] We applaud the guideline endorsement for earlier combination therapy.[1] Conversely, we disagree with the implied notion that all combinations of first-line agents are equal and should be prescribed at provider discretion. The available evidence supports that CCB/ACEI yields the greatest cardiovascular protection in higher-risk patients and those with stage 2 hypertension.[2–5] Given these proven benefits and the low potential for risk, we propose that hypertension management can be simplified and optimized by adopting a streamlined strategy starting with CCB/ACEI for most patients.

## ARTICLE INFORMATION

### Correspondence

Robert D. Brook, MD, Division of Cardiovascular Diseases, Wayne State University, 400 Mack Avenue, 2nd Floor, Detroit MI 48201. Email brook@wayne.edu

### Affiliations

Division of Cardiovascular Diseases (R.D.B.), Department of Emergency Medicine and Integrative Biosciences Center (P.D.L.), Wayne State University, Detroit, MI. Division of Cardiovascular Medicine, University of Michigan, Ann Arbor (K.A.J.).

### Disclosures

K.A.J. is a site investigator for Finerenone in a diabetic nephropathy clinical trial (Bayer). The other authors report no conflicts.

## REFERENCES

1. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2018;138:e426–e483. doi: 10.1161/CIR.0000000000000597
2. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med.* 2008;359:2417–2428. doi: 10.1056/NEJMoa0806182
3. Brook RD, Weder AB. Initial hypertension treatment: one combination fits most? *J Am Soc Hypertens.* 2011;5:66–75. doi: 10.1016/j.jash.2011.01.002
4. Brook RD, Kaciroti N, Bakris G, Dahlöf B, Pitt B, Velazquez E, Weber M, Zappe DH, Hau T, Jamerson KA. Prior medications and the cardiovascular benefits from combination angiotensin-converting enzyme inhibition plus calcium channel blockade among high-risk hypertensive patients. *J Am Heart Assoc.* 2018;7:e006940. doi: 10.1161/JAHA.117.006940
5. Brook RD, Kaciroti N, Bakrisk G, Dahlöf B, Pitt B, Velazquez E, Weber MA, Jamerson KA; ACCOMPLISH Investigators. Cardiovascular benefits of angiotensin converting enzyme inhibition plus calcium channel blockade in patients achieving tight blood pressure control and with resistant hypertension [published online November 20, 2020]. *Am J Hypertension*. doi: 10.1093/ajh/hpaa192