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Is Choice of Antihypertensive Agent Important in Improving Cardiovascular Outcomes in High-Risk Hypertensive Patients?

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Hypertension currently affects more than 25% of the world's population and its prevalence is increasing.¹ By the year 2025, nearly 1 in 3 adults worldwide (approximately 1.56 billion people) are projected to have hypertension.¹ Hypertension accounts for 64 million disability adjusted life-years and is the third most important cause of global burden of disease in the general population.² As one of the leading risk factors for increased cardiovascular morbidity and mortality, hypertension is an important treatable public health problem. Therefore, research identifying how to manage hypertension to improve cardiovascular outcomes is of global importance. Many randomized controlled trials have demonstrated blood pressure (BP) lowering in hypertensive individuals improves cardiovascular outcomes.^{3–6} More recently, studies comparing specific therapeutic agents have raised the hypothesis that certain classes of antihypertensive agents may confer cardiovascular protection beyond their effects on BP lowering. The Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT) was one such trial. ALLHAT demonstrated equivalence of a thiazide-type diuretic as compared to an angiotensin converting enzyme inhibitor (ACE-I) and a calcium channel blocker (CCB) in terms of heart attack.⁷ An important lesson from this trial was that a substantial proportion of hypertensive individuals require more than one antihypertensive agent to achieve BP goals promulgated in clinical practice guidelines.⁸ This has led to the notion that combinations of antihypertensive agents may be desirable for managing hypertension, particularly in high-risk individuals. The ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) study, published in 2008 in the *New England Journal of Medicine*, shed new light on combination therapies for the treatment of hypertension.⁹

WHAT DOES THIS IMPORTANT STUDY SHOW?

The ACCOMPLISH trial sought to determine whether combination drug therapy with an ACE-I and a CCB was superior to the combination of an ACE-I and a thiazide diuretic for reducing cardiovascular events in high-risk hypertensive participants. The ACCOMPLISH trial was a multicenter international double-blind, industry sponsored study which

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randomized 11,506 participants to one of 2 treatment arms: benazepril plus amlodipine or benazepril plus hydrochlorothiazide. All enrolled patients had hypertension and were at high-risk (including a history of coronary events, myocardial infarction, revascularization, stroke, impaired kidney function, peripheral artery disease, left ventricular hypertrophy, or diabetes) for cardiovascular events. In both arms, benazepril was titrated from 20 to 40 mg and thereafter, amlodipine was increased from 5 to 10 mg or hydrochlorothiazide was increased from 12.5 mg to 25 mg to reach a target BP of <140/90 mm Hg (or <130/80 mm Hg in participants with diabetes or kidney disease). The primary endpoint was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, resuscitation after cardiac arrest, or coronary revascularization. The final study cohort had a mean age of 68.4 years, 60.4% of participants had diabetes, and 6.1% had “renal disease” (defined as a serum creatinine >1.5mg/dl in women or >1.7mg/dl in men or the presence of macroalbuminuria confirmed on 2 separate occasions). The mean follow-up was 35 months and the mean systolic and diastolic BPs after dose adjustments were 131.6/73.3 mm Hg in the benazepril-amlodipine arm vs 132.5/74.4 mm Hg in the benazepril-hydrochlorothiazide arm (a difference in systolic BP of 0.9 mm Hg and diastolic BP of 1.1 mm Hg). The trial was stopped early based on prespecified stopping rules due to a significant difference in cardiovascular events between the 2 treatment arms. The primary endpoint occurred in 9.6% of participants in the benazepril-amlodipine arm and 11.8% of participants in the benazepril-hydrochlorothiazide arm, representing an absolute risk reduction of 2.2 percentage points and a relative risk reduction of 19.6% (HR of 0.80, $p<0.001$). The secondary endpoint of death from cardiovascular causes and nonfatal myocardial infarction and stroke also showed a benefit with benazepril-amlodipine vs benazepril-hydrochlorothiazide. It is important to note that hospitalization for congestive heart failure was not a component of the primary or secondary endpoint, however the addition of congestive heart failure events to the primary endpoint did not alter the results. The cumulative rate of discontinuation of a study drug was similar between arms (28.8% and 31.2% in the benazepril-amlodipine and the benazepril-hydrochlorothiazide arms, respectively). The most common reason for discontinuing study drug was an adverse event which occurred in 13.4% of participants in the benazepril-amlodipine arm and 14.3% of participants in the benazepril-hydrochlorothiazide arm. While the occurrence of adverse events was similar between groups overall, peripheral edema appeared to occur more commonly in participants in the benazepril-amlodipine vs benazepril-hydrochlorothiazide arm (31.2% vs 13.4%, respectively).

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

First, it is important to point out that in comparing ACCOMPLISH with prior trials one must keep in mind the unique design of ACCOMPLISH, in particular the use of a combination pill. The key objective of ACCOMPLISH was to determine whether CCBs added to an ACE-I vs a thiazide added to an ACE-I would be superior. No other studies have made such comparison. In contrast to ACCOMPLISH, previous studies comparing CCB to other antihypertensive agents have failed to demonstrate differences in cardiovascular outcomes when equal BPs were achieved in each arm (examples include STOP_[A1]-2, INVEST, and INSIGHT) (See Table 1). STOP-2 (Swedish Trial in Old Patients with Hypertension-2) was

an open label, blinded endpoint trial that compared diuretics/ β -blockers to ACE-I or CCB in 6614 elderly hypertensive patients. Achieved BP was approximately 159/80 mmHg in all arms of the study and there was no difference between the 3 groups on the composite endpoint of fatal stroke, fatal myocardial infarction and other fatal cardiovascular disease.¹⁰ INVEST (International Verapamil-Trandolapril Study) compared verapamil to atenolol (with add on of trandolapril and or hydrochlorothiazide) among 22,576 patients with hypertension and coronary heart disease.¹¹ The achieved BP was similar between groups throughout the study; however, there was no difference in the primary outcome (composite of death, nonfatal myocardial infarction, or nonfatal stroke) between participants randomized to verapamil vs atenolol. INSIGHT (Intervention as a Goal in Hypertension Treatment) was a double blind randomized trial of 6321 hypertensive patients with at least one cardiovascular risk factor assigned to nifedipine or hydrochlorothiazide/amiloride.¹² BP control was similar between groups and there was no difference between groups in the primary endpoint of cardiovascular death, myocardial infarction, heart failure or stroke; however, fatal myocardial infarction and non-fatal heart failure occurred more frequently in the nifedipine arm.

In those studies where the achieved BP was higher with CCB vs other agents, cardiovascular outcomes were either equivalent or worse with CCB (examples include ALLHAT and the Nordic Diltiazem [NORDIL] study, see Table 1). The NORDIL trial compared diltiazem to a combination of diuretic/ β -blocker in 10,916 hypertensive participants.¹³ The BP achieved during the study despite adding on other antihypertensive agents was higher in the diltiazem group (155/89 mm Hg vs 152/89 mm Hg) and there was no difference in the primary endpoint of cardiovascular events between groups. ALLHAT compared chlorthalidone to amlodipine and lisinopril in 33,357 hypertensive patients with at least one coronary heart disease risk factor.⁷ Achieved BP was higher in participants treated with amlodipine (0.8 mm Hg) and lisinopril (2.0 mm Hg) compared to participants treated with chlorthalidone. There was no difference in the primary endpoint of cardiovascular events between the 3 arms. However, there was a higher rate of congestive heart failure with amlodipine vs diuretic.

Trials which achieved better BP control with CCB vs other agents have demonstrated similar or better cardiovascular outcomes with CCB (examples include VALUE and ASCOT). The VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) trial was a double-blind randomized industry sponsored trial comparing valsartan to amlodipine in 15,245 hypertensive participants at high cardiovascular risk.¹⁴ There was no difference in the primary composite endpoint of fatal and nonfatal cardiovascular events including heart failure, myocardial infarction, and cardiac interventions. BP control was better in the amlodipine arm (by 2–4 mmHg systolic) and secondary endpoints including stroke and myocardial infarction were lower in the amlodipine vs valsartan arm. ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) was a randomized open-label industry sponsored study of amlodipine +/- perindopril vs atenolol +/- diuretic in 19,257 patients with hypertension and at least 3 other cardiovascular risk factors.¹⁵ Systolic BP was 2.7 mm Hg lower with amlodipine-based regimen vs atenolol-based regimens and the trial was stopped early due to higher mortality with the atenolol-diuretic regimen. While there was no difference in the primary endpoint of non-fatal

myocardial infarction and fatal coronary heart disease after final data analysis, the amlodipine-perindopril arm had decreased cumulative incidences of stroke, cardiovascular mortality and all-cause mortality. However, secondary analyses of VALUE and ASCOT-BPLA suggest the differences in clinical outcomes in these studies were partially attributed to differences in BP between treatment arms.^{16,17}

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The ACCOMPLISH trial is the first large-scale outcome trial to demonstrate a beneficial effect of the combination of an ACE-I and a CCB as compared to an ACE-I and a thiazide diuretic in high-risk hypertensive participants. The findings from this unique study strongly suggest that for those who are candidates for multiple antihypertensive agent treatment, that the ACE-I/CCB combination is a very reasonable, if not preferable, first choice. Prior studies did not directly compare combinations of an ACE-I with either a CCB or thiazide diuretic. Prior studies (STOP-2, INVEST, ALLHAT, INSIGHT, NORDIL) which compared CCB to nonCCB therapy did not find a benefit with CCB over other agents when similar BP or higher BP was achieved with CCB vs non CCB. However, the ASCOT trial, the VALUE trial and ACCOMPLISH study demonstrated somewhat better BP control with CCB-based regimens and subsequent improvement in cardiovascular outcomes. In light of these trials and meta-analyses of these trials,^{3,6} it is evident that the initial choice of a single antihypertensive agent is less important than the ability to achieve target BP in an individual patient. Considering this, the American Heart Association, the European Society of Hypertension, and the European Society of Cardiology guidelines on the management of hypertension agree that thiazide diuretics, β -blockers, CCBs, ACE-I and angiotensin receptor blockers all can adequately lower BP and reduce cardiovascular outcomes and all are suitable for the initiation and maintenance of antihypertensive treatment either as monotherapy or in combination.^{18,19} Whether the ACCOMPLISH trial results will influence future recommendations for BP lowering in high-risk hypertensive patients when more than one agent is needed to achieve BP goal remains to be determined.

While none of the reviewed trials had a high proportion of patients with chronic kidney disease, the results from multi-drug combination studies are particularly relevant in this population given the increased number of antihypertensive agents required to control BP. Considering ACCOMPLISH and other studies demonstrated favorable BP control with the use of CCB, an initial choice of ACE-I/CCB is a good therapeutic option with the caveat that diuretics are often also required to control BP in advanced stages of chronic kidney disease. An analysis of BP control and kidney function in the subgroup of ACCOMPLISH trial participants with chronic kidney disease at entry might inform future clinical practice guidelines for management of hypertension in chronic kidney disease.

In summary, adequate control of BP remains an important means towards lowering cardiovascular morbidity and mortality in high-risk individuals. Choice of antihypertensive therapy should continue to be individualized and tailored toward balancing maximal BP control with encouraging patient adherence to treatment regimens and minimizing unfavorable side effects.

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Table 1

Summary of clinical trials comparing calcium channel blockers to other agents

Study	Design	Intervention	Patient Population	Primary Outcome	Achieved BP or BP reduction (mmHg)	Results of Primary Endpoint
STOP-2 ¹⁰	Open label RCT	Diuretics/ β -blockers vs ACE-I vs CCB	6,614 pts (70–84 y) w/HTN	Fatal stroke, fatal MI, or other CV disease	158/81 vs 159/81 vs 159/80	No difference
INVEST ¹¹	Open label RCT	Verapamil +/- trandolapril vs atenolol +/- HCTZ	22,576 pts w/HTN & CAD	Death, nonfatal MI, or nonfatal stroke	Decrease in systolic BP of 18.7 vs 19.0	No difference
INSIGHT ¹²	Double blind RCT	Nifedipine vs HCTZ/amiloride	6,321 pts (55–80 y) w/HTN & at least 1 CV risk factor	CV death, MI, heart failure or stroke	138/82 in both arms	No difference
NORDIL ¹⁴	Open label RCT	Diltiazem vs B-blockers vs B-blocker/diuretic	10,881 pts (50–74 y) w/HTN	Fatal and nonfatal stroke, fatal and non-fatal MI, or other CV death	155/89 vs 152/89	No difference
ALLHAT ⁷	Double blind RCT	Chlorthalidone vs amlodipine vs lisinopril	33,357 pts w/HTN & at least 1 CHD risk factor	Fatal coronary heart disease or nonfatal MI	systolic BP of 133.9 vs 134.7 vs 135.9	No difference
VALUE ¹⁴	Double blind RCT	Valsartan vs amlodipine	15,245 pts w/HTN & high CV risk	Fatal and nonfatal heart failure, MI, and cardiac interventions	systolic BP of 139.3 vs 137.5	No difference
ASCOT-BPLA ¹⁵	Open label RCT	Amlodipine perindopril vs atenolol +diuretic	19,257 pts w/HTN & at least 3 other CV risk factors	Nonfatal MI and fatal CHD	systolic BP of 136.1 vs 137.7	No difference but study stopped early due to higher death in atenolol arm

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ALLHAT, Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm trial; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CHD, coronary heart disease; CV, cardiovascular; HCTZ, hydrochlorothiazide; HTN, hypertension; INVEST, International Verapamil-Trandolapril Study; INSIGHT, Intervention as a Goal in Hypertension Treatment study; MI, myocardial infarction; NORDIL, Nordic Diltiazem study; pts, patients; RCT, randomized controlled trial; STOP-2, Swedish Trial in Old Patients with Hypertension-2; VALUE, Valsartan Antihypertensive Long-Term Use Evaluation trial