Article Type: Original Article

Subject category: Hypertension

Prior Medications and the Cardiovascular Benefits from Combination Angiotensin Converting Enzyme Inhibition plus Calcium Channel Blockade among High-Risk Hypertensive Patients

Running title: *Brook et al.; Prior Medications and Anti-Hypertensive Therapy*

Robert D. Brook MD[1], Niko Kaciroti PhD[2], George Bakris MD[3], Björn Dahlöf MD PhD[4], Bertram Pitt MD[1], Eric Velazquez MD[5], Michael Weber MD[6], Dion H. Zappe PhD[7], Tsushung Hau PhD[7] and Kenneth A. Jamerson MD[1]

[1]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI; [2]Center for Human Growth and Development and Department of Biostatistics, University of Michigan, Ann Arbor, MI; [3]The University of Chicago Medicine, Chicago, IL; [4]Sahlgrenska University Hospital Östra, Göthenburg, Sweden; [5]Duke University School of Medicine, Durham, NC; [6]State University of New York Downstate, Brooklyn, NY; [7]Novartis Pharmaceuticals, East Hanover, NJ

Correspondence:

Robert D. Brook, MD

24 Frank Lloyd Wright Dr. PO Box 322

Ann Arbor, MI. 48106; (734) 998-5627; robdbrok@umich.edu

Division of Cardiovascular Medicine, University of Michigan

Abstract Word Count: 248; Body Word Count: 2509

Journal Subject Terms: Hypertension, Treatment, Clinical Studies**Abstract**

Background: The ACCOMPLISH trial demonstrated that combination therapy using amlodipine rather than hydrochlorothiazide in conjunction with benazepril provided greater cardiovascular risk reduction among high-risk hypertensive patients. Few trials have evaluated the effect of prior antihypertensive therapy used among participants on the study outcomes.

Methods and Results: In a post hoc observational analysis, we examined the characteristics of the drug regimens taken prior to trial enrollment in the context of the primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac death, and coronary revascularization). In the "primary subgroup" (n=4475), patients previously taking any renin-angiotensin system blockade plus either a diuretic or a calcium channel blocker alone or as part of their anti-hypertensive regimen), there were 206/2193 (9.4%) versus 281/2282 (12.3%) primary composite events among those randomized to combination therapy involving amlodipine versus hydrochlorothiazide, respectively (adjusted Cox proportional hazard ratio: 0.74, 95% confidence interval 0.62 to 0.89, p=0.0015). All other participants (n=6975) previously taking any antihypertensive regimen not included in the primary subgroup also benefited from randomization to amlodipine plus benazepril (adjusted Hazard Ratio: 0.84, 95% confidence interval: 0.72-0.98, p=0.024). Outcomes among most other subgroups, including patients previously taking lipid-lowering medications or dichotomized by prior blood pressure-control status, showed similar results.

Conclusions: When combined with an angiotensin converting enzyme inhibitor, amlodipine provides cardiovascular risk reduction superior to hydrochlorothiazide largely regardless of prior medication usage. These findings add further support for the initial usage of this combination regimen among high-risk hypertensive patients.

Key words: blood pressure; hypertension; risk; cardiovascular disease; therapy

Clinical Perspective

What is new?

● When combined with an angiotensin converting enzyme inhibitor, amlodipine provided superior cardiovascular risk protection compared to hydrochlorothiazide irrespective of what blood pressure-lowering agents were used in the past.

What are the clinical implications?

● As the majority of hypertensives (≥75%) require ≥2 medications to achieve blood pressure goals, our observations support that most patients should consider treatment with a renin-angiotensin system blocker combined with a calcium channel blocker as first-line therapy or as part of the overall therapeutic regimen (if additional drugs are still required) even if other antihypertensive agent(s) were used in the past.

● A streamlined strategy of starting initial combination therapy using a renin-angiotensin system blocker combined with a calcium channel blocker should be should be tested versus current hypertension guidelines in a clinical outcome trial for the prevention of cardiovascular events.

Antihypertensive therapy is well-established to reduce the adverse cardiovascular consequences of high blood pressure (BP)[1]. The overall evidence supports that the degree of BP-lowering is the major determinant of the health benefits[1]. Guidelines therefore emphasize the importance of controlling BP as the preeminent goal[2,3]. In this regard, it is important to acknowledge that most hypertensive patients (e.g., 75%) require ≥ 2 antihypertensive medications to achieve BP targets[4]. As such, the most germane issue to explore to guide present-day clinical practice is which combination of medications (rather than what single agent) provides optimal cardiovascular protection[5]. While most patients in clinical trials were taking more than one anti-hypertensive medication,[1] only the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension) study was designed to investigate the comparative cardiovascular risk reductions derived from two pre-specified combination regimens prescribed as initial therapy[6]. The study was

terminated early (mean follow-up of 36 months) due to the superiority of benazepril (B) + amlodipine (A) compared to B + hydrochlorothiazide (H) for preventing the primary composite outcome (hazard ratio (HR): 0.80, 95% confidence interval (CI), 0.72 to 0.90; p<0.001). Subsequent analyses showed that this benefit occurred among patients with coronary artery disease[7] and diabetes[8], was superior for preventing adverse renal outcomes[9], and was not likely a consequence of subtle BP differences between groups (ambulatory BP monitoring)[10].

As with most contemporary trials[1], most patients (97.1%) entering into the ACCOMPLISH study had already been receiving antihypertensive therapy[6]. Hence, the main conclusion of the study can most accurately be stated as: switching treated hypertensive individuals to initial combination therapy comprised of B+A rather than B+H is more effective for preventing cardiovascular events. Due to this high rate of background therapies, it is important to evaluate if the characteristics of the prior regimens had a modifying effect on study outcomes. For example, some medication(s) may have differed in reducing baseline cardiovascular risk (e.g., superior 24-hour BP control, fewer adverse metabolic actions) and could have thereby plausibly impacted the capacity for the ensuing randomized treatments to differentially provide cardiovascular protection. The principal aim of this post hoc observational analysis was to determine if combination therapy using B+A conveys a significant risk reduction on the primary composite endpoint in a subgroup of patients who had already been taking a drug regimen similar to either of the treatment limbs allocated in the trial ("primary subgroup"): renin angiotensin system (RAS) blockade plus either a thiazide-type diuretic or any calcium channel blocker (CCB) alone or as part of their anti-hypertensive regimen. This is a clinically-relevant question because both combination therapy regimens remain recommended approaches by guidelines[2,3] and are considered rational pharmacological strategies[4] commonly employed in present-day practice. In secondary analyses, we explored if prior usage of other anti-hypertensive regimens, background lipid-lowering therapy, or previous BP control status may have modified the benefits derived from allocation to B+A.

Methods

The overall design and methods of the ACCOMPLISH trial have been previously described[6]. The institutional review boards or ethics committees of each participating site approved the protocol as described in the primary manuscript[6]. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. In brief, ACCOMPLISH was an international (5 countries), multicenter (n=548) double-blind randomized clinical outcome trial of 11056 patients with hypertension at high risk for cardiovascular disease. The primary outcome was time to first composite event (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac death, and coronary revascularization) compared between treatment limbs (B+A versus B+H). In this post hoc observational analysis, we aimed to evaluate the effect of prior medication regimens on the primary study outcome. Prior to undertaking the analyses, we a priori defined the "primary subgroup" as patients previously taking a regimen similar to either randomized treatment subsequently allocated in trial. This included individuals on a RAS-blocker (any angiotensin converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB]) plus either a thiazide-like diuretic or CCB. The two anti-hypertensive medications could be taken alone (i.e., no additional BP medications) or as part of a larger regimen (≥ 3 drugs in total) including any supplementary BP-lowering medications (e.g., beta blockers, alpha blockers). We began the series of analyses with and highlighted the presentation of our findings in this "primary subgroup" because we felt the results from these patients would yield the overall most clinically-relevant information. These findings specifically inform health care providers the sum benefits together of maintaining a RAS-blocker/CCB regimen if already taking it as well as switching to this regimen among patients taking a RAS-blocker/diuretic regimen. Subsequent analyses further evaluated the individual benefits in each of these subgroups alone, along with several other groups with a viable sample size.

Statistical Methods

The hazard ratios (HRs) and corresponding 95% confidence intervals (95% CI) related to allocation to B+A versus B+H were assessed among individual subgroups of

participants previously treated with various anti-hypertensive and other medication regimens upon entering the trial using survival analyses with Cox proportional hazard models. Specifically, the Cox models comparing the effectiveness of randomized treatments were separately evaluated in each of the specified subgroups of participants. The HRs in the Cox models were adjusted for baseline age, smoking status, history of prior myocardial infarction, coronary revascularization, hospitalization for unstable angina, baseline systolic and diastolic blood pressure, and left ventricular hypertrophy (LVH) by ECG (co-variables related to the primary endpoint). All other subgroups evaluated were analyzed as secondary endpoints by adjusted Cox proportional hazard models and confined to groups >700 patients as smaller sample sizes could yield unstable or unreliable results. Kaplan-Meier estimates with the log-rank test were also used to estimate and compare the endpoints throughout the trial for the two treatment groups. In addition to performing individual subgroup analyses, we also tested for effect modification on the HRs (by prior treatment subgroup identifier) in the entire cohort of patients. This was done by adding an interaction term of the subgroup indicator and treatment indicator in the Cox model that included all study participants.

Results

The characteristics of the overall ACCOMPLISH study cohort (n=11506) have been previously described[6]. Table 1 presents the results separated into 2 sub-groups: the "primary subgroup" (n=4475) versus "all other participants" (n=6975 individuals not on a regimen containing a RAS-blocker plus either a diuretic or CCB upon enrollment). There were 56 participants not taking any BP medication upon enrollment in the trial who were not included in our current study, giving us a total sample size of 11450. There were some small but statistically significant differences in characteristics between subgroups. However, this is not relevant in regards to the objectives of this study, which aimed to assess the efficacy of B+A in both groups, irrespective of potential differences in characteristics.

The following results are from the individual subgroup analyses. In the primary subgroup, there were 206/2193 (9.4%) composite study events among individuals randomized to B+A versus 281/2282 (12.3%); in those allocated to B+H (adjusted

hazard ratio [HR]: 0.74, 95% CI: 0.62 to 0.89, p=0.0015) (Figure 1). In all other participant sub-groups, those assigned to B+A (adjusted HR: 0.84, 95% CI: 0.72-0.98, p=0.024) also benefited (Figure 2). Confining the analyses to a "limited primary subgroup" including individuals previously taking a 2-drug regimen consisting of only a RAS-blocker plus either a thiazide-like diuretic or CCB (i.e., no additional anti-hypertensive agent of any class in their regimen) yielded similar results. In this limited primary subgroup (n=2266), there were 97/1140 (8.5%) composite study events among individuals randomized to B+A versus 117/1126 (10.4%) in those allocated to B+H (adjusted hazard ratio [HR]: 0.80 95% CI: 0.61 to 1.04, p=0.099). Given the similar HR to that of the primary subgroup, the borderline non-significant p-value is likely due to a smaller sample size. All other participants not in the limited primary subgroup (n=9184) also benefited from assignment to B+A (HR: 0.80, 95% CI: 0.70-0.91, p=0.0006). Controlling for achieved BP levels at 6-months into the trial did not substantively alter the results for any of the above subgroups.

Though not always statistically significant, the HRs also favored randomization to B+A for most other subgroups in secondary analyses based upon pre-enrollment or background drug regimens, including those taking lipid-lowering medications or with a systolic BP< 140 mm Hg upon study enrollment (Figure 3). With one exception (ACEI + CCB), the rates of the main composite endpoints were similar across subgroups within the same treatment limb, ranging from 8.9%-9.8% and 9.9%-16.0% for B+A versus B+H, respectively. Composite endpoint rates were higher in the B+H compared to the B+A treatment limb in all subgroups (Table 2).

The following results are for the model involving the entire cohort of patients that included an interaction term to test for effect modification on the HRs by subgroups (prior treatments). Other than for the ACEI + CCB subgroup, there was no evidence of effect modification (non-significant interaction terms) on the main composite endpoint for any other subgroup evaluated (Table 3). To explore for reasons underlying the greater benefit in the ACEI+CCB subgroup, we evaluated for differences in characteristics among these participants (Table 4). Though some clinical variables were statistically different, adding these to model did not eliminate the significance of the

interaction term (p=0.006). Controlling for achieved BP levels at 6-months into the trial also did not substantively alter these findings.

Discussion

The main finding of this post hoc observational analysis of the ACCOMPLISH trial is that patients who were previously receiving a combination anti-hypertensive regimen similar to either treatment limb used in the study (i.e., RAS-blocker + diuretic or CCB) derived cardiovascular benefit from allocation to B+A. The risk reduction for the composite endpoint was similar in this "primary subgroup" (26%) than among "all other participants" (15%) and in the overall trial cohort (20%)[6]. This suggests that cardiovascular protection can be improved not only by switching patients on a RAS-blocker + diuretic to combination therapy using B+A, but also by continuing the latter regimen among individuals already receiving it. These findings are relevant to present-day clinical practice because both regimens remain advocated as viable strategies by recent guidelines[2-4] for patients requiring combination therapy to achieve BP control[6-10].

No subgroup appeared to be harmed (all HRs <1.0) by allocation to B+A including those previously taking any anti-hypertensive regimen other than those used in the primary subgroup, those on background cholesterol-lowering agents, and patients with systolic BP already controlled to target goal (Figure 3). It is possible that some of the HRs may not have reached traditional levels of significance principally due to reduced statistical power given the smaller subgroup sample sizes. Nonetheless, in each scenario the risk reductions trended in favor of B+A. There was also no evidence of significant effect modification of any subgroup on the main composite outcome except for greater benefit among those previously taking an ACEI + CCB (Tables 2 and 3). The reasons for this latter observation are not clear; however, it further supports maintaining this regimen among those already receiving it.

Clinical Implications

Taken together with previous ACCOMPLISH study results[6], our current findings add support to the contention that high-risk hypertensive patients will likely benefit, or at the very least will not be harmed, by converting their BP-lowering regimen to

combination therapy using B+A. This applies to diabetics, patients with coronary heart disease, and those at risk for adverse renal outcomes[6-10]. In the present analysis, even individuals with controlled hypertension (i.e., systolic BP <140 mm Hg) or taking only a single antihypertensive agent benefitted (or trended towards benefit).

Greater BP-lowering efficacy of B+A is unlikely to explain its superiority since 24-hour ambulatory levels did not differ between treatment limbs in a subgroup analysis (n=573) of participants ACCOMPLISH[10]. We have previously reviewed several hypotheses including therapeutic reasons (e.g., reduced drug-related side effects, better compliance) and biological mechanisms (e.g., greater central aortic BP-lowering) plausibly responsible for the greater cardiovascular risk reduction derived from initial combination therapy using B+A as opposed to other regimens[5]. Nevertheless, the underlying explanation(s) for these current findings as well as the main ACCOMPLISH results must remain speculative at the present time.

The evidence from several trials[11,12] and observational analyses[13] supports that starting a 2-drug regimen (i.e., "initial" combination therapy) rather than a single anti-hypertensive agent can not only achieve more rapid and superior BP control,[4] but may also lead to better cardiovascular outcomes[14]. These prior studies demonstrated the benefits of initial combination therapy a variety of regimens. Given the superiority of B+A versus B+H (even among patients taking at least 2 BP medications[6]), we posit that initial combination therapy specifically with RAS-blockade plus CCB (when clinically-appropriate and not contra-indicated) may be an even more effective management strategy for the prevention of cardiovascular events than estimated by prior combination therapy studies[11-14].

Strengths and Limitations

We are aware of only one prior analysis from a major hypertension trial (VALUE) in which the impact on study outcomes was evaluated in relation to prior BP-lowering treatment regimens[15]. As with ACCOMPLISH, most study patients (92%) had been receiving antihypertensive therapy prior to entering the VALUE trial. In accordance with our findings, the study endpoints were not differentially impacted by prior medications. This is a particularly relevant issue for contemporary clinical practice because the vast

majority of patients among modern trials had been already undergoing treatment with medications[1].

We acknowledge that our results derive from post hoc observational analyses and as such must be considered hypothesis-generating. Nevertheless, the consistency of responses favoring B+A among all subgroups supports the overall veracity of our overarching contention. Additionally, our findings only directly apply to high-risk individuals given the characteristics of the patients in ACCOMLISH[6]. Whether or not the results can be extrapolated to other and lower-risk patients is unknown; however, recent evidence supports that medical treatment is likely beneficial even for low risk patients with mild hypertension[1]. Positive findings in our study were observed in patients previously taking a number of single BP-lowering medications and those with systolic BP <140/90 mm Hg, supporting the hypothesis that even individuals with milder forms of high BP may benefit from B+A. The average on-treatment BP ACCOMPLISH was below 140/90 mm Hg. Thus, any speculations of the merits of initiating combination therapy with B+A implicitly presume that this regimen is capable of keeping BP controlled (alone or with additional agents as needed). This is particularly important given the recent results of the SPRINT trial, which also supports a lower systolic BP target (120 mm Hg) than previously espoused[16]. Patients were allocated to a subgroup based upon the medications they were taking right at the time of study enrollment. The duration they had been treated with these agents, prior medication usage in the years beforehand, as well as their adherence to this regimen remain unknown. However, since most subgroups derived similar relative benefits from B+A, it is not likely that any unaccounted for changing of prior medications between the various regimens in the months-to-years prior to entering the trial would have differentially impacted the treatment effects of the combination therapy regimens used in the ACCOMPLISH trial in a manner that explains our current findings. Finally, we were not able to explain the significantly greater benefit of B+A in the ACEI+CCB subgroup (Table 3). It remains possible that unaccounted for factors (i.e., not listed in Table 4) could have led to a propensity to receive ACEI+CCB combination and thus explains the greater benefit in this one subgroup.

Conclusions

High risk hypertensive patients achieved a greater cardiovascular risk reduction by allocation to B+A as compared to B+H largely regardless of their prior medication treatment regimens, baseline BP control status, and background lipid-lowering therapies. Our findings add further support that most hypertensives should strongly consider combination RAS-blocker/CCB as first-line therapy.

Funding Sources: The original ACCOMPLISH trial was funded by Novartis Pharmaceuticals.

Disclosures: GB reports clinical trials for Bayer and consulting for Takeda Pharmaceuticals, AbbVie, CVRx, Janssen, Eli Lilly and Company/Boehringer-Ingelheim, Medtronic, Astra-Zeneca, Novartis, GSK, Bayer, and Daichi-Sankyo. BP reports consulting for Bayer, Merck, Astra Zeneca, Boehringer Ingelheim, Forrest Laboratories, Relypsa, scPharmaceuticals, PharMain, Tricida, DaVinci Biosciences, Stealth Peptides, KBP BioSciences, and AuraSense. He reports stock options in Relypsa, scPharmaceuticals, PharMain, KBP BioSciences, AuraSense, DaVinci Biosciences, Galectin Therapeutics, Tricida; patent pending: site-specific delivery of eplerenone to the myocardium. DSMBs: Novartis Pharmaceuticals, Inc, J&J, Oxygen Biotherapeutics;and is on the events committee for Juventis. EV reports consulting for Novartis, Amgen, and Merck and has received grant support from the National Heart, Lung, and Blood Institute, Novartis, Amgen, Pfizer, Alynylam, Medtronic Foundation. DHZ is an employee of Novartis Pharmaceuticals, Inc. TH is an employee of Novartis Pharmaceuticals, Inc. MAW reports consulting for Boehringer Ingelheim, Eli Lilly and Company, Forest and speaking for Arbor Pharmaceuticals. KAJ reports clinical trials (Bayer). The remaining authors have no disclosures to report.

References:

1. Zanchetti A, Thomopoulos C, Parati G. Randomized controlled trials of blood pressure lowering in hypertension: a critical reappraisal. Circ Res 2015; 116: 1058-73.
2. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311: 507-20.
3. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31: 1281-357.
4. Gradman AH, Basile JN, Carter BL, Bakris GL; American Society of Hypertension Writing Group. Combination therapy in hypertension. J Am Soc Hypertens 2010; 4: 42-50.
5. Brook RD, Weder AB. Initial hypertension treatment: one combination fits most? J Am Soc Hypertens 2011; 5: 66-75.
6. 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: 2417-28.
7. Bakris G, Briasoulis A, Dahlof B, Jamerson K, Weber MA, Kelly RY, Hester A, Hua T, Zappe D, Pitt B; ACCOMPLISH Investigators. Comparison of benazepril plus amlodipine or hydrochlorothiazide in high-risk patients with hypertension and coronary artery disease. Am J Cardiol 2013; 112: 255-9.

8. Weber MA, Bakris GL, Jamerson K, Weir M, Kjeldsen SE, Devereux RB, Velazquez EJ, Dahlöf B, Kelly RY, Hua TA, Hester A, Pitt B; ACCOMPLISH Investigators. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol 2010; 56: 77-85.
9. Bakris GL, Sarafidis PA, Weir MR, Dahlöf B, Pitt B, Jamerson K, Velazquez EJ, Staikos-Byrne L, Kelly RY, Shi V, Chiang YT, Weber MA; ACCOMPLISH Trial investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. Lancet 2010; 375: 1173-81.
10. Jamerson KA, Bakris GL, Weber MA. 24-hour ambulatory blood pressure in the ACCOMPLISH trial. N Engl J Med 2010; 363: 98.
11. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SA, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. Hypertension 2009; 53: 646-53.
12. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM.Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet 2011; 377: 312-20.
13. Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial monotherapy and combination therapy and hypertension control the first year. Hypertension 2012; 59: 1124-31.
14. Gradman AH, Parisé H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. Hypertension 2013; 61: 309-18.
15. Zanchetti A, Julius S, Kjeldsen S, McInnes GT, Hua T, Weber M, Laragh JH, Plat F, Battegay E, Calvo-Vargas C, Cieslinski A, Degaute JP, Holwerda NJ, Kobalava J, Pedersen OL, Rudyatmoko FP, Siampooulos KC, Sotset O. Outcomes in subgroups of hypertensive patients treated with regimens based upon valsartan and amlodipine: an analysis of findings from the VALUE trial. J Hypertens 2006; 24: 2163-8.

16. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015; 373: 2103-16.

Figure Legends:

Figure 1. Composite trial outcomes in the primary subgroup. Survival curves amongst individuals in the primary subgroup: previously taking an antihypertensive regimen consisting of any renin-angiotensin system (RAS) blocker (angiotensin converting enzyme inhibitor or angiotensin receptor blocker) plus (either a diuretic or calcium channel blocker) as part of their anti-hypertensive regimen who were randomized to B+A (solid line) versus B+H (broken line). P-value is for HR by log-rank test. B, benazepril; A, amlodipine; H, hydrochlorothiazide; HR, hazard ratio, No. number.

Figure 2. Composite trial outcomes among all other participants not in the primary subgroup. Survival curves amongst all other individuals not in the primary subgroup who were randomized to B+A (solid line) versus B+H (broken line). P-value is for HR by log-rank test. B, benazepril; A, amlodipine; H, hydrochlorothiazide; HR, hazard ratio, No. number.

Figure 3. Composite trial outcomes among additional secondary subgroups. Forest plot representing the adjusted hazard ratios ± 95% confidence intervals by Cox proportional hazard model in favor of B+A therapy by secondary subgroups. In each anti-hypertensive medication subgroup, participants were taking the specific medication(s) listed without over-lap between unique subgroups. Patients could not be included in more than one subgroup. For example, patients in the CCB alone, ACEI alone, (ACEI + CCB), and (ACEI + diuretic) subgroups were all different individuals. The

exception is that there were overlaps in patients between subgroups containing the term "or" in the definition. For example, patients could be in both the (ACEI + diuretic) group as well as the [(ACEI or ARB) + diuretic] subgroup. Patients using other anti-hypertensive agents not listed in the figure (e.g., beta blockers, alpha blockers) were not excluded from these subgroups. Other subgroups listed include background lipid-lowering therapy and systolic blood pressure control status upon trial randomization. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HMG CoA, hydroxy-methyl-glutaryl-coenzyme-A reductase inhibitor (statin); mod, modifying; SBP, systolic blood pressure.

Table 1. Characteristics of the participants in the main subgroups (total n = 11450)

Subject Characteristics	Primary Subgroup	All other participants	p-value
Subjects – n (%)	4475 (39.1%)	6975 (60.9%)	
Sex - n (%)			<0.0001
Male	2686 (60.0%)	4256 (61.0%)	
Female	1789 (40.0%)	2719 (39.0%)	
Age - mean ± SD	68.2 ± 6.9	68.4 ± 6.9	0.102
≥ 65 years - n (%)	2948 (65.9%)	4652 (66.7%)	0.366
≥ 70 years	1812 (40.5%)	2864 (41.1%)	0.545
Race or ethnic group - n (%)			0.081
Black	615 (13.7%)	757 (10.9%)	<0.0001
White	3682 (82.3%)	5919 (84.9%)	.0003
Hispanic	237 (5.3%)	385 (5.5%)	0.607
Other	164 (3.7%)	264 (3.8%)	0.741
Region - n (%)			<0.0001
United States	3288 (73.5%)	4809 (69.0%)	
Nordic Countries	1187 (26.5%)	2166 (31.0%)	
Anthropometrics			
Weight (kg)	89.8 ± 18.9	87.8 ± 19.0	<0.0001
Waist circumference (cm)	104.7 ± 15.3	103.3 ± 15.3	<0.0001
Body mass index (Kg/m^2)	31.4 ± 6.2	30.6 ± 6.2	<0.0001
Medications - n (%)			
Lipid-lowering agents	3933 (68.4%)	4662 (67.6%)	0.359
Beta-blockers	1930 (43.5%)	3451 (50.1%)	<0.0001
Anti-platelets agents	2794 (63.0%)	4374 (63.5%)	0.641
Hemodynamics			
Systolic BP (mm Hg)	144.8 ± 18.1	145.8 ± 18.4	0.007
Diastolic BP (mm Hg)	79.3 ± 10.7	80.5 ± 10.7	<0.0001
Heart rate (beats/min)	70.7 ± 10.9	70.2 ± 11.0	0.026

Laboratory values			
Creatinine (mg/dL)	1.0 ± 0.28	0.98 ± 0.26	0.0006
Glucose (mg/dL)	128.6 ± 45.5	126.6 ± 46.9	0.033
Potassium (mmol/dL)	4.2 ± 0.4	4.3 ± 0.4	<.0001
Total cholesterol (mg/dL)	183.4 ± 38.9	185.1 ± 40.1	0.046
HDL-C (mg/dL)	49.3 ± 13.9	49.5 ± 14.1	0.401
Risk factors - n (%)			
Myocardial infarction	948 (21.2%)	1755 (25.2%)	<0.0001
Stroke	565 (12.6%)	928 (13.3%)	0.293
Hospitalization for USA	475 (10.6%)	848 (12.2%)	0.012
Diabetes mellitus	2897 (64.7%)	4007 (57.5%)	<0.0001
Renal disease	319 (7.1%)	383 (5.5%)	0.0004
Coronary revascularization	1495 (33.4%)	2612 (37.5%)	<0.0001
CABG	869 (19.4%)	1570 (22.5%)	<0.0001
PCI	814 (18.2%)	1359 (19.5%)	0.085
Other			
LVH	573 (13.1%)	954 (14.0%)	0.172
Current smoking	492 (11.0%)	803 (11.5%)	0.393
Dyslipidemia	3373 (75.4%)	5160 (74.0%)	0.094
Atrial fibrillation	297 (6.6%)	479 (6.0%)	0.632

BP, blood pressure; HDL-C, high density lipoprotein cholesterol; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LVH, left ventricular hypertrophy.

Table 2. Composite primary event rates in the treatment limbs for each subgroup

Study sub-group	B+A limb Events (%)	B+H limb Events (%)
ACEI + CCB (n=1375)	60 (8.88%)	112 (16.0%)
ACEI + Diuretic (n=1419)	64 (9.40%)	79 (10.7%)
(ACEI or ARB) + Diuretic (n=2745)	124 (9.25%)	151 (10.75%)
ARB + Diuretic (n=1326)	60 (9.19%)	72 (10.79%)
ACEI Alone (n=2562)	127 (9.67%)	136 (10.9%)
(ACEI or ARB alone) or [(ACE or ARB) + Diuretic] (n=6336)	295 (9.37%)	340 (10.65%)
Not: [(ACEI or ARB) + (CCB or Diuretic)] (n=6975)	323 (9.16%)	372 (10.77%)
CCB Alone (n=717)	35(9.49%)	40(11.5%)
ACEI or ARB Alone (n=3591)	171 (9.46%)	189 (10.58)
ARB Alone (n=1032)	44(8.91%)	53(9.85%)
Statin only or with other lipid-lowering drug (n=7635)	365 (9.75%)	462 (11.87%)
Baseline systolic BP ≥ 140 mm Hg (n=6977)	327 (9.44%)	426 (12.13%)
Baseline systolic BP < 140 mm Hg (n=4480)	202 (8.96%)	227 (10.2%)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker

Table 3. Significance of the interaction terms for effect modification for each subgroup on the hazard ratio between study treatment limbs

Study sub-group	p-value for interaction term
ACEI + CCB (n=1375)	0.005
ACEI + Diuretic (n=1419)	0.844
(ACEI or ARB) + Diuretic (n=2745)	0.688
ARB + Diuretic (n=1326)	0.739
ACEI Alone (n=2562)	0.431
(ACEI or ARB) + (CCB or Diuretic) (n=4475)	0.307
Not: (ACEI or ARB) + (CCB or Diuretic) (n=6975)	0.307
CCB Alone (n=717)	0.752
ACEI or ARB Alone (n=3591)	0.383
ARB Alone (n=1032)	0.797
Statin only or with other lipid-lowering drug (n=7635)	0.769
Baseline systolic BP ≥ 140 mm Hg (n=6977)	0.551
Baseline systolic BP < 140 mm Hg (n=4480)	0.551

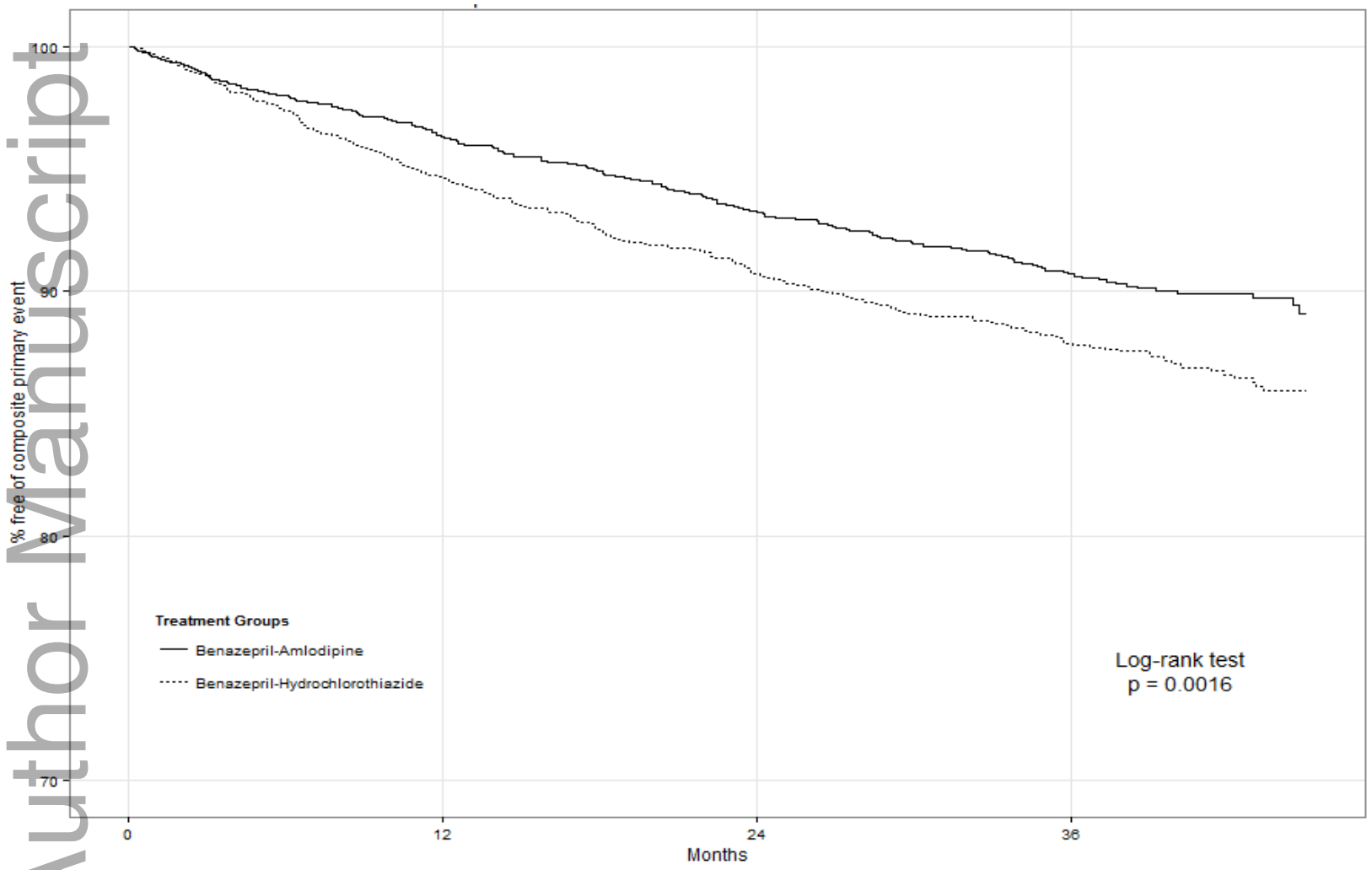
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker. Model adjusted for: baseline age, smoking status, history of prior myocardial infarction, coronary revascularization, hospitalization for unstable angina, systolic and diastolic BP, and left ventricular hypertrophy

Table 4. Characteristics of the study participants in the ACEI+CCB subgroup versus all other participants

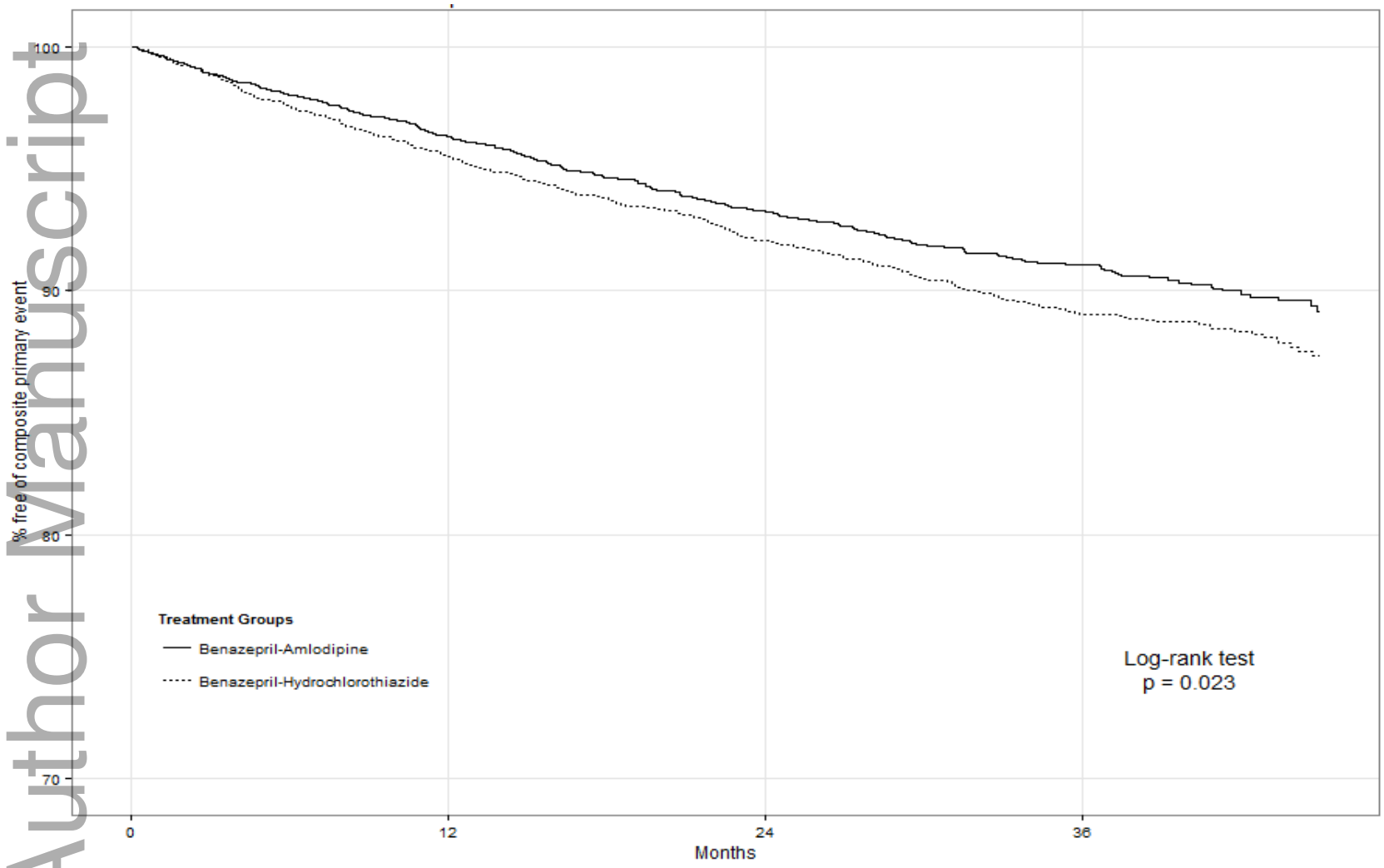
Subject Characteristics	ACEI+CCB	All other participants	p-value
Subjects – n (%)	1375 (12.0%)	10075 (88.0%)	
Sex - n (%)			0.121
Male	860 (62.6%)	6082 (60.4%)	
Female	515(37.5%)	3993 (39.6%)	
Age - mean ± SD	68.4 ± 7.1	68.4 ± 6.8	0.996
≥ 65 years - n (%)	897 (65.2%)	6703 (66.5%)	0.341
≥ 70 years	563 (41.0%)	4113 (40.8%)	0.931
Race or ethnic group - n (%)			0.0002
Black	242 (17.6%)	1130 (11.2%)	<0.0001
White	1074 (78.1%)	8527 (84.6%)	<0.0001
Hispanic	85 (6.2%)	537 (5.3%)	0.191
Other	54 (3.9%)	374 (3.7%)	0.693
Region - n (%)			<0.0001
United States	1138 (82.8%)	6959 (69.1%)	
Nordic Countries	237 (17.2.5%)	3116 (30.9%)	
Anthropometrics			
Weight (kg)	89.0 ± 19.0	88.5 ± 18.9	0.396
Waist circumference (cm)	104.0 ± 16.2	103.8 ± 15.2	0.714
Body mass index (Kg/m^2)	31.1 ± 6.2	30.9 ± 6.2	0.354
Medications - n (%)			
Lipid-lowering agents	939 (68.9%)	6756 (67.8%)	0.393
Beta-blockers	584 (42.9%)	4797 (48.1%)	0.0003
Anti-platelets agents	876 (64.3%)	6292 (63.1%)	0.396
Hemodynamics			
Systolic BP (mm Hg)	144.7 ± 17.9	145.5 ± 18.3	0.131
Diastolic BP (mm Hg)	79.0 ± 10.6	80.2 ± 10.8	0.0002
Heart rate (beats/min)	70.8 ± 10.7	70.3 ± 11.0	0.126
Laboratory values			
Creatinine (mg/dL)	0.97 ± 0.28	0.99 ± 0.27	0.055
Glucose (mg/dL)	128.4 ± 48.0	127.3 ± 46.1	0.431

Potassium (mmol/dL)	4.3 ± 0.4	4.3 ± 0.4	0.535
Total cholesterol (mg/dL)	183.5 ± 38.2	184.5 ± 39.8	0.418
HDL-C (mg/dL)	49.6 ± 14.2	49.4 ± 14.0	0.788
Risk factors - n (%)			
Myocardial infarction	294 (21.4%)	2409 (23.9%)	0.038
Stroke	188 (13.7%)	1305 (13.0%)	0.457
Hospitalization for USA	166 (12.1%)	1157 (11.5%)	0.522
Diabetes mellitus	851 (61.9%)	6053 (60.1%)	0.198
Renal disease	118 (8.6%)	584 (5.8%)	<0.0001
Coronary revascularization	512 (37.2%)	3595 (35.7%)	0.260
CABG	315 (22.9%)	2124 (21.1%)	0.121
PCI	275 (20.0%)	1898 (18.8%)	0.303
Other			
LVH	176 (13.2%)	1351 (13.7%)	0.586
Current smoking	157 (11.4%)	1138 (11.3%)	0.893
Dyslipidemia	1060 (77.1%)	7473 (74.2%)	0.02
Atrial fibrillation	90 (6.6%)	686 (6.8%)	0.715

BP, blood pressure; HDL-C, high density lipoprotein cholesterol; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LVH, left ventricular hypertrophy.



No. at risk				
B+A	2282	2120	1982	1198
B+H	2193	2068	1958	1184



No. at risk

B+A	3452	3215	3015	1741
B+H	3523	3310	3131	1848