Efficacy and Duration of Benazepril Plus Amlodipine or Hydrochlorthiazide on 24-Hour Ambulatory Systolic Blood Pressure Control

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Abstract—The combination of benazepril plus amlodipine was shown to be more effective than benazepril plus hydrochlorothiazide in reducing cardiovascular events in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial. There was a small difference in clinic systolic blood pressure between the treatment arms favoring benazepril plus amlodipine. Ambulatory blood pressure monitoring provides a more rigorous estimate of blood pressure effects. A subset of 573 subjects underwent ambulatory blood pressure monitoring during year 2. Readings were obtained every 20 minutes during a 24-hour period. Between-treatment differences (benazepril plus amlodipine versus benazepril plus hydrochlorothiazide) in mean values were analyzed using ANOVA. Treatment comparisons with respect to categorical variables were made using Pearson's χ^2. At year 2, the treatment groups did not differ significantly in 24-hour mean daytime or nighttime blood pressures (values of 123.9, 125.9, and 118.1 mm Hg for benazepril plus amlodipine group versus 122.3, 124.1, and 116.9 for the benazepril plus hydrochlorothiazide group), with mean between-group differences of 1.6, 1.8, and 1.2 mm Hg, respectively. Blood pressure control rates (24-hour mean systolic blood pressure $<$130 mm Hg on ambulatory blood pressure monitoring) were greater than 80% in both groups. Nighttime systolic blood pressure provided additional risk prediction after adjusting for the effects of drugs. The 24-hour blood pressure control was similar in both treatment arms, supporting the interpretation that the difference in cardiovascular outcomes favoring a renin angiotensin system blocker combined with amlodipine rather than hydrochlorothiazide shown in the ACCOMPLISH trial was not caused by differences in blood pressure, but instead intrinsic properties (metabolic or hemodynamic) of the combination therapies. **(*Hypertension*. 2011;57:174-179.)**

Key Words: hypertension ■ clinical trial ■ ambulatory blood pressure monitoring ■ clinical outcomes ■ calcium channel blocker therapy

Hypertension remains a leading cause of morbidity and mortality globally.[1] While lowering blood pressure with any effective therapy reduces cardiovascular (CV) risk, the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial recently reported additional benefit attributable to a specific combination of antihypertensive medications. In particular, the combination of benazepril plus amlodipine (B+A) was superior to the combination of benazepril plus hydrochlorothiazide (B+H) in reducing CV disease events in high-risk hypertensive subjects.[2] The 2 regimens utilized in the trial achieved similar levels of blood pressure assessed by conventional blood pressure measurements (mean systolic difference measured in the clinic [0.9 mm Hg difference overall and 0.7 mm Hg at year 2]).

Twenty-four-hour ambulatory blood pressure measurement (ABPM) contributes more measurements and information than clinic readings and thus is a better reflection of true overall blood pressure.[3,4] When compared with clinic readings, ABPM is a better predictor of target organ damage.[5,6] Variations in the 24-hour blood pressure profile, including the absence of the normal fall in blood pressure during sleep (nondippers) or an excessive surge in blood pressure when awakening, provide additional measures of CV risk.[7–11]

The primary results of the ACCOMPLISH study raised speculation that the 2 treatment regimens may have exerted

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different effects on the 24-hour blood pressure profile.[12] While both amlodipine and hydrochlorothiazide provide peak plasma concentrations within 2 hours after ingestion, the plasma half-life of hydrochlorothiazide is 12 to 15 hours[13] contrasted to the half-life of amlodipine of 28 to 30 hours.[14] Conceivably, the hydrochlorothiazide group might have been at a disadvantage because of increased rates of escape from control at nighttime or increased surges in blood pressure during the early morning hours.[15] Moreover, previous CV event trials in hypertension utilized hydrochlorothiazide at higher doses (50 to 100 mg) than the 25 mg in the ACCOMPLISH study, or used a thiazide-like agent such as chlorthalidone with a longer duration of effect.[16]

To resolve some of these potential issues, an ABPM substudy was nested within the ACCOMPLISH trial to ascertain whether differences existed in the ability of the 2 combination treatment regimens, B+A and B+H, to achieve full 24-hour blood pressure control after 2 years of treatment.

Methods

A total of 11 506 patients were randomized in the ACCOMPLISH trial, with ≈70% from the United States and the remainder from the Nordic region of Europe. The ABPM substudy was prospectively designed and implemented in 74 US sites. Only patients enrolled in the United States were eligible to participate. Detailed eligibility criteria for the overall cohort have been described previously.[17] All participants provided written informed consent.

Participants

A total of 790 participants were recruited for this cohort. Baseline ABPM measures were made in 218 participants, and 573 had an ABPM measurement during the second year (the time point of the primary analysis) of the study (1 subject had both). Only participants with measures made during year 2 are included in the current analysis.

Procedures

Spacelabs Medical ambulatory blood pressure monitors (model 9029718) were used. Participants wore the ABPM device for a minimum of 24 hours with automatic readings every 20 minutes.[18] Nondominant arm, adult large or normal cuffs were utilized; initial clinic versus ambulatory readings were within 5 mm Hg of each other; time of placement of the monitors was during the medication trough period; and only subjects with 80% success were included.

Clinic blood pressure measurements were made at the investigational site using a calibrated standard sphygmomanometer or a calibrated digital device. At each study visit, after having the patient in a sitting position for 5 minutes, systolic/diastolic blood pressure and heart rate were scheduled to be measured 3 times at 1- to 2-minute intervals. The average of the last 2 readings was taken at the clinic reading.

Statistical Analysis

Power and Sample Size

The sample size calculation for the ambulatory blood pressure monitoring subset was based on the primary ABPM parameter of interest: 24-hour mean ambulatory systolic blood pressure (ASBP). Assuming a 10% dropout rate, a total sample size of n=560 randomized patients (ie, 510 completed patients and 255 per treatment group) was required. This sample size was based on detecting a difference in 24-hour ASBP of 2.5 mm Hg (±10 mm Hg) with 80% power, assuming 2-sided significance tests at the 5% level.

Analysis

Hourly mean ASBP values at year 2 were calculated by taking the average of the corresponding readings (every 20 minutes) during each hourly interval after the ABPM recording device start time. Twenty-four-hour ambulatory blood pressure values were calculated for each patient by taking the average of the corresponding available hourly mean values.

Twenty-Four-Hour ABPM Definitions (Derived From O'Brien et al[4])

Daytime was defined as 10 AM through 9 PM, and nighttime was defined as 1 AM through 6 AM. Dippers were defined as patients whose mean nighttime systolic blood pressure (SBP) was at least 10% below the patient's mean daytime values. The AM surge occurred if there was a rise of >55 mm Hg (during the hours of 6 to 10 AM) when compared to the subject's lowest nighttime (>12 to ≤6 AM) hourly mean ASBP value.

Between-treatment differences in absolute ambulatory mean values (and in absolute clinic values) were analyzed using ANOVA with treatment as a factor.

Between-treatment differences with respect to incidence of the primary composite CV end point at true end were compared for patients with year 2 ABPM measurements using Kaplan–Meier curves and the log-rank test. The primary composite CV end point was defined as time to the first event among the adjudicated events: CV death, stroke, myocardial infarction, resuscitated sudden death, hospitalization for unstable angina, and coronary revascular procedure (coronary artery bypass graft or percutaneous coronary intervention).

Treatment comparisons with respect to control rates and other categorical variables (eg, percentage of dippers, AM surge) were made using Pearson's χ^2 statistic. Two Cox regression analyses were performed to assess residual effects of daytime, nighttime, and 24-hour mean blood pressure after adjustment for drug treatment.

In 1 analysis, each variable was examined separately after adjusting for treatment effect. In the other analysis, stepwise Cox regression was used, in which treatment effect was kept in the analysis model and all other blood pressure measurements were selected for inclusion in the model if $P<0.25$ and were allowed to stay in the model if $P<0.15$. Variables in the final model were considered significant if $P<0.05$.

Results

Baseline Characteristics

The baseline characteristics of patients in the 2 treatment groups with ABPM measurements during year 2 of treatment are shown in Table 1. The cohort was predominately male (64%) and Caucasian (89%), and the mean age of the cohort was 68.4 years. All subjects were treated with antihypertensive medication prior to study entry. Overall, there were no significant differences in the baseline characteristics between the 2 treatment groups in the ABPM study. Moreover, the 24-hour ABPM cohort did not differ on baseline characteristics substantially from the global ACCOMPLISH cohort.

Effects of 2 Years of Treatment on Clinic and 24-Hour ABPM

Clinic Blood Pressure Measurements

Clinic SBP at baseline was similar in the treatment groups (141.5 for B+A versus 140.2 for B+H; difference of 1.3 mm Hg) (baseline table). The corresponding clinic SBP values after 2 years of drug treatment were 129.3 for B+A and 129.9 for B+H with a difference of −0.6 mm Hg that was not statistically significant (Table 2).

Twenty-Four-Hour Blood Pressure Measurements

The mean 24-hour systolic and diastolic blood pressure patterns after 2 years of combination therapy are shown in Figure 1 for treatments B+A and B+H. Comparisons of

Table 1. Baseline Demographics in the Ambulatory Blood Pressure Cohort in ACCOMPLISH

Characteristics	B+A (n=288)	B+H (n=285)	Parent Population (Global Cohort) (n=11 506)
Male/female	185/103 (64.2/35.8)	186/99 (65.3/34.7)	6963/4542 (60.5/39.5)
Ethnicity			
Black	23 (8.0)	20 (7.0)	1416 (12.3)
Caucasian	254 (88.2)	255 (89.5)	9612 (83.5)
Other	11 (3.8)	10 (3.5)	477 (4.1)
Age, year	68.4 (6.60)	68.5 (6.37)	68.4 (6.86)
BMI, kg/m^2	30.8 (6.26)	30.6 (5.38)	30.9 (6.23)
GFR*, mL/min per 1.73 m^2	80.6 (23.65)	80.3 (21.72)	79.0 (21.34)
MSSBP, mm Hg	141.5 (16.32)	140.2 (15.42)	144.7 (18.23)
MSDBP, mm Hg	78.2 (10.09)	77.8 (10.57)	79.7 (10.78)
No. of drugs at baseline	2.34	2.30	…

Values are numbers (percentage) of patients. BMI indicates body mass index; GFR, glomerular filtration rate; MSDBP, mean sitting diastolic blood pressure; MSSBP, mean sitting systolic blood pressure.

*Modification of diet in renal disease formula.

clinic SBP, 24-hour systolic ambulatory blood pressure, daytime systolic ambulatory blood pressure, and nighttime systolic ambulatory blood pressure after 2 years of treatment are shown in Table 2.

The between-group differences in 24-hour readings (after 2 years of treatment) of 1.6, 1.8, and 1.2 mm Hg for the mean 24-hour, daytime, and nighttime readings, respectively, were not statistically significant, but there was a slightly higher blood pressure in the amlodipine group compared to the hydrochlorothiazide group.

Comparisons of 24-Hour Ambulatory Profile and Control Rates After 2 Years of Treatment

Table 3 compares the treatment groups based on characteristics of the 24-hour SBP profile. The numbers of subjects classified as dippers (29% in the B+A group and 32% in the B+H group) were similar between the 2 groups. Nearly 11% of subjects had escape from control of SBP >160 mm Hg (10.4% in the B+A group and 11.9% of the B+H group). Control rates (24-hour ABPM mean <135/85) were similar and exceeded 80% in both treatment groups.

Figure 2 shows the effect of the drug treatment on the primary CV outcome for this small cohort of 573 subjects with ABPM. The beneficial effect observed in the original cohort in favor of the combination of amlodipine and benazepril compared to hydrochlorothiazide and benazepril was again observed in the ABPM cohort (hazard reduction of 39%, log-rank $P=0.057$).

When assessing residual effects of blood pressure on the primary CV end point using a Cox proportional hazard model after adjusting for the treatment group effect alone, 24-hour, nighttime, and clinic SBPs at year 2 were significant predictors of primary events. In a stepwise regression model, nighttime SBP at year 2 was a significant predictor of the primary CV event when adjusting for treatment effect, while clinic SBP at year 2 was a significant predictor when not adjusting for treatment effect.

Table 2. Mean Ambulatory Systolic and Diastolic Blood Pressure (in mm Hg) After 2 Years of Treatment by Treatment Group in ACCOMPLISH

Blood Pressure Characteristics	B+A (n=288)	B+H (n=285)	Mean Difference
Clinic	129.3	129.9	−0.6
24 Hours	123.9	122.3	1.6
Daytime	125.9	124.1	1.8
Nighttime	118.1	116.9	1.2

Daytime, 10 AM to 9 PM; nighttime, 1 to 6 AM.

Discussion

The ABPM study of the ACCOMPLISH trial was designed to assess the adequacy and duration of SBP control with the 2 combination treatment regimens over the 24-hour dosing interval. Both B+A and B+H achieved 24-hour blood pressure control rates of >80%. Moreover, both regimens were able to sustain SBP control over the entire 24-hour period for the majority of patients.

In this current report, we find small differences in the mean SBP measured in the clinic at both baseline and after 2 years of treatment; while not statistically significant, the amlodipine group had trend for lower clinic blood pressure. However, after 2 years of treatment, 24-hour mean SBP measures were not significantly different in the 2 treatment arms when measured by ABPM. Moreover, there was a small advantage that trended in favor of the hydrochlorothiazide combination (24-hour means: 122.3 mm Hg for B+H versus 123.9 mm Hg for B+A). The finding that 24-hour blood pressure levels are not substantially different in the 2 regimens supports the original interpretation of the ACCOMPLISH investigators that the difference in the primary CV end point that favored the amlodipine-based regimen was not caused by blood

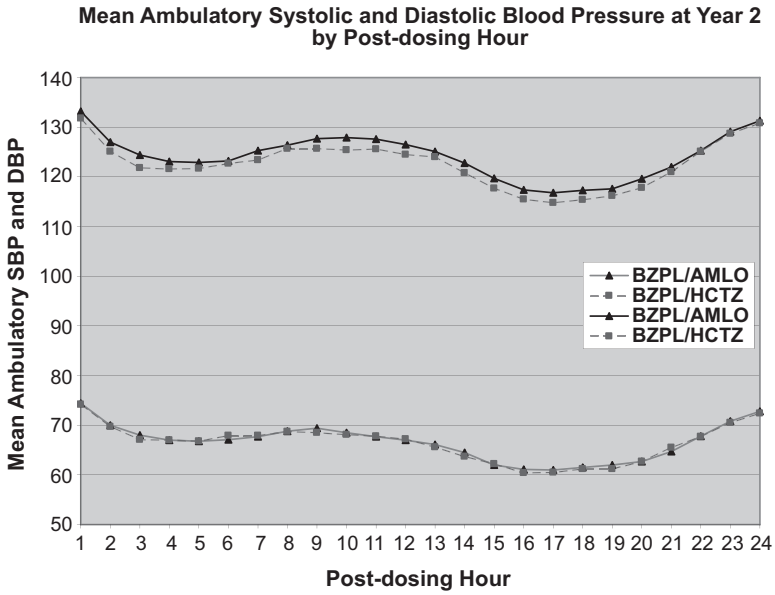

Figure 1. Mean hourly blood pressure values in 573 subjects by drug assignment (the average of readings made every 20 minutes) during the 24-hour dosing interval. BZPL indicates benazepril; AMLO, amlodipine; HCTZ, hydrochlorothiazide; DBP, diastolic blood pressure.

pressure differences but, rather, by other putative cardioprotective properties of the combination of a renin angiotensin system blocker with amlodipine.

Thiazide diuretics have been and will likely remain a cornerstone in the management of hypertension. Hypertension guidelines consider both thiazide and thiazide-like diuretics as interchangeable effective agents.[19–21] The original report of the ACCOMPLISH investigators showing the benefit of the amlodipine-based regimen compared with the hydrochlorothiazide-based regimen raised the question of whether this particular diuretic was an appropriate choice. The Multiple Risk Factor Intervention Trial used both hydrochlorothiazide and chlorthalidone in the same trial, although assignment of patients to these treatments was by investigator choice, not randomization.[22] In a retrospective analysis, research sites that chose hydrochlorothiazide had higher CV mortality rates compared with chlorthalidone. In addition, chlorthalidone has demonstrated CV protection in other major trials.[23,24]

In the overall cohort of the ACCOMPLISH trial, we previously reported a small but statistically significant greater reduction in SBP with the combination of amlodipine and benazepril as well as a 20% risk reduction in CV events. There is a trend for a lower CV event rate in the B+A therapy group in the ABPM cohort despite its small sample size. This analysis is limited by low study power and by a survival bias (only subjects alive and healthy enough to have the tracing made at year 2 were included). After adjusting for the effect of drug treatment, nighttime SBP provided additional prediction of CV risk. The use of ABPM provides unique blood pressure information for the management of high-risk hypertensive patients.

Table 3. Twenty-Four-Hour Blood Pressure Profiles and Blood Pressure Control Rates After 2 Years of Treatment

Ambulatory Characteristics	B+A (n=288)	B+H (n=285)	All (n=573)	*P* Value
Dipper	29.2	31.6	30.4	0.530
Nondipper	70.8	68.4	69.6	…
Control at 2 years (ABMP <135/85 mm Hg)	81.3	84.9	83.1	0.243
Any hourly mean SBP reading >160 mm Hg	10.4	11.9	11.2	0.565
Nighttime hypertension >130 mm Hg	18.8	18.6	18.7	0.962
Morning surge*	2.8	3.5	3.1	0.616

Values are percentage of patients.

*More than 55 mm Hg rise between 6 and 10 AM compared to lowest nighttime hourly mean.

The present study establishes that hydrochlorothiazide in a maximum dose of 25 mg is fully as effective in reducing blood pressure as a maximum 10-mg dose of amlodipine when combined with the same renin angiotensin system blocker. Moreover, this efficacy of hydrochlorothiazide was sustained across the full dosing interval. Clearly, the longer plasma half-life of amlodipine did not confer any blood pressure advantages over hydrochlorothiazide on the absolute values or profiles of the 24-hour blood pressure.

Perspectives

The use of either hydrochlorothiazide or amlodipine in combination with benazepril as an initial blood pressure strategy is a paradigm shift in clinical trials that provides exceptional blood pressure control. Accordingly, initial combination therapy may gain favor as an approach for prompt and safe reduction in blood pressure. The ACCOMPLISH investigators reported a 20% risk reduction in CV events with amlodipine rather than hydrochlorothiazide. These novel data have important implications for millions of patients taking diuretics as initial therapy who may potentially gain less CV protection but also endure the untoward effects including gout and increased incidence of diabetes. Criticism was leaved on our choice of diuretic. Many event trials used chlorthalidone (hydrochlorothiazide was used in ACCOMPLISH and by at least 85% of practicing clinicians). Controversy was predicated on hydrochlorothiazide and chlorthalidone monotherapy data emphasiz-

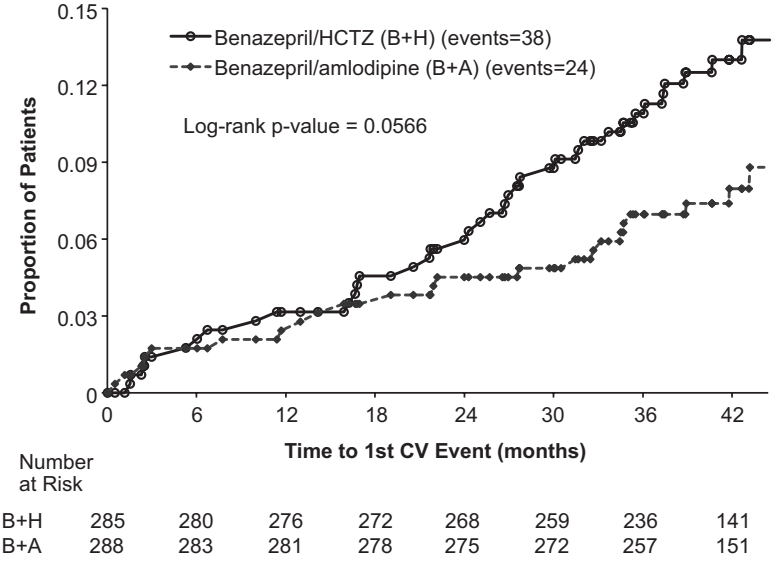

Figure 2. The primary composite CV end point was defined as time to the first event among the adjudicated events: CV death, stroke, myocardial infarction, resuscitated sudden death, hospitalization for unstable angina, and coronary revascular procedure (coronary artery bypass grafting or percutaneous coronary intervention) in the 573 subjects participating in the ABPM substudy. HCTZ indicates hydrochlorothiazide.

ing the longer duration of the effect of chlorthalidone on blood pressure control. Some even postulated that if chlorthalidone were used in ACCOMPLISH, the outcomes might have been different. This speculation will never be fully answered, as ACCOMPLISH was intentionally designed as a combination therapy trial. However, our current results do provide AMBP data demonstrating that amlodipine (with a plasma half-life even longer than that of chlorthalidone) provided no long-term blood pressure advantage over hydrochlorothiazide when both were used in combination with benazepril. We raise the possibility that some property other than the half-life of the drugs confers significant cardio-protection in ACCOMPLISH. Ultimately, we find no reason to prefer diuretics (not even chlorothalidone) as first-line or initial therapy.

Conclusion

The combination of amlodipine with blockade of the renin angiotensin system could emerge as a leading strategy for both control of blood pressure and reduction of CV events.[25] The fact that over 80% of patients achieved ABPM control in both arms demonstrates that combination therapy is effective in getting patients to the goal. Ultimately, however, we find no evidence to support the recommendation to prefer a diuretic-based combination regimen as initial therapy in the treatment of high-risk hypertension.

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