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Review Article

Effects of amlodipine and other classes of antihypertensive drugs on long-term blood pressure variability: Evidence from randomized controlled trials

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Abstract

Blood pressure (BP) is monitored and managed to prevent cardiovascular complications of hypertension, but BP variability (BPV) has not been sufficiently studied. This analysis assessed whether patients receiving amlodipine vs other antihypertensive agents had lower BPV after ≥12 weeks of treatment. Studies were included if individual subject data were available, had ≥1 active comparator, and treatment duration was ≥12 weeks. BPV was assessed using standard deviation (SD) and coefficient of variation (CV) of systolic BP across visits from 12 weeks. Individual trial and meta-analyses were performed for SD- and CV-based methodology. Five studies (47,558 BPV-evaluable patients) were included. Patient characteristics were largely consistent across the studies, but BP measurements varied from ∼4 months to ∼6 years. BPV with amlodipine was significantly ($P < .0001$) lower vs atenolol and lisinopril; significantly ($P < .0001$) lower than enalapril in one study and numerically, but not significantly lower in another; and similar to chlorthalidone and losartan. Meta-analysis revealed a treatment difference (standard error) for amlodipine vs all active comparators of −1.23 (0.46; $P = .008$) mm Hg using SD and −0.86 (0.31; $P = .005$) using CV. These findings suggest that amlodipine is effective for minimizing BPV. Future studies need to confirm a causal link between BPV and cerebrovascular/cardiovascular outcomes. J Am Soc Hypertens 2014;8(5):340–349.

Keywords: Blood pressure variability; calcium channel blockers; hypertension; meta-analysis; trial.

Introduction

Hypertension is an important public health challenge worldwide. The benefit of reducing blood pressure (BP) levels in patients with hypertension to prevent cardiovascular events is well proven.[1,2] BP goals for patients with hypertension (with or without added cardiovascular risk) are well defined in current management guidelines.[1,3] In the clinical setting, absolute BP levels are typically used as a therapeutic target to prevent stroke and coronary heart disease; however, BP fluctuation across visits and its impact on disease has generally not been studied. Current hypertension guidelines also dismiss BP fluctuations (or ''episodic hypertension'') as not requiring treatment.[3–7]

BP variability (BPV) has been observed both over a 24-hour period, with ambulatory BP monitoring showing reading-to-reading variability, and between-clinic visit fluctuations (visit-to-visit variability) in the short- and long-term.[8] BPV is common; in a cohort of patients with previous transient ischemic attacks (TIAs), only 12% had stable hypertension, and 69% had episodic hypertension (some with systolic BP [SBP] readings ≤140 mm Hg, and some with

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SBP readings >140 mm Hg).[9] Increased 24-hour BPV has been associated with cardiovascular damage,[10] and visit-to-visit systolic BPV is a strong predictor for stroke in patients with hypertension.[9] In the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure-Lowering Arm) trial of 19,257 patients aged 40 to 79 years with hypertension and at least three other cardiovascular risk factors, visit-to-visit systolic BPV on treatment (atenolol- and amlodipine-based regimens) was a strong predictor of stroke and coronary events, independent of mean levels of clinic or ambulatory SBP.[9] Results from the United Kingdom transient ischemic attack (UK-TIA) aspirin trial (in patients with a recent TIA) and three validation TIA and minor stroke cohorts (ESPS-1 [European Stroke Prevention Study], Dutch TIA trial, and ASCOT-BPLA)[9] revealed that visit-to-visit systolic BPV, independent of mean SBP, was a strong predictor of subsequent stroke. Long-term BPV also increases cerebrovascular risk. For example, the WHICAP (Washington Heights-Inwood Columbia Aging Project), an epidemiologic study of 686 subjects aged ≥65 years, showed that the risk of cerebrovascular disease increased with increasing BP and BP fluctuation.[11]

Reducing BP fluctuation, as well as mean BP, has recently been recognized as a potential target for improved management of hypertension to prevent cardiovascular events, particularly stroke.[9,12] Consequently, the effect of currently available antihypertensive agents on BPV is now garnering interest. Amlodipine is a well-established, long-acting calcium channel blocker (CCB) that effectively reduces BP in hypertension.[13] In the X-CELLENT study (n = 577), 24-hour ambulatory BP measurement before and after 3 months' treatment showed that amlodipine decreased daytime, nighttime, and 24-hour systolic BPV, whereas candesartan did not.[14]

The objective of this analysis was to explore whether patients taking amlodipine had lower BPV compared with those taking a range of other antihypertensive agents after ≥12 weeks of treatment. This analysis also examined if the trend of BPV (amlodipine vs other antihypertensive agents) after ≥12 weeks of treatment was consistent across different patient subgroups. This study is unique and adds substantially to the current literature, because it provides individual subject BPV data.

Methods

Study Design

In this retrospective analysis, studies involving amlodipine were selected for inclusion from the Pfizer Internal Database for amlodipine if individual patient level data were available, the study had at least one active antihypertensive therapy comparator arm, and the treatment duration was at least 12 weeks. Five studies, that is, ASCOT-BPLA,[15,16] ALLHAT (Antihypertensive & Lipid Lowering Treatment to Prevent Heart Attack Trial),[17] CAMELOT (Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis),[18] NY92011, and R-0510 (Table 1), fulfilled these selection criteria and were analyzed for BP and visit-to-visit BPV. Patients who received at least one dose of antihypertensive drug and had at least two post-baseline SBP measurements from 12 weeks (or 3 months or 84 days) onwards were included in the analysis and constituted the BPV-evaluable population. Data from the BPV population from the five studies were analyzed individually and in a meta-analysis.

Definition of BPV

The definitions of BPV were within-subject standard deviation (SD) and coefficient of variation (CV) of SBP measurements across visits from 12 weeks (or 3 months or 84 days) onwards. Where SBP measurements from sitting or standing positions were available, measurements from the sitting position were used in preference.

Individual Study Analysis

BPV data were summarized and compared between treatment groups using the analysis of variance model. The model included a factor for treatment group. Least squares (LS) means and standard errors (SE) were derived for each treatment group. 95% confidence intervals (CIs) were constructed for the LS mean of each treatment group and for the difference in LS means obtained from comparison of amlodipine with other antihypertensive agents. Subgroup analyses for the BPV data were conducted by age (<65 or ≥65 years) and race. The data were also analyzed adjusting for mean SBP values across visits from 12 weeks (or 3 months or 84 days [ie, that used to calculate the BPV measurement]) using the analysis of covariance (ANCOVA) model. The impact of baseline SBP on BPV was investigated using an ANCOVA model adjusting for baseline SBP values. Analyses were repeated for SD- and CV-based BPV data. The SBP data were summarized and analyzed using the ANCOVA model including the baseline SBP value as the covariate.

Meta-analysis

Meta-analysis of four treatment comparisons was conducted by combining estimates of treatment differences derived from individual study analyses. The four treatment comparisons were: amlodipine vs the angiotensin-converting enzyme (ACE) inhibitor, enalapril (two studies: CAMELOT and NY92011); amlodipine vs ACE inhibitors (enalapril and lisinorpril; three studies: CAMELOT, NY92011, and ALLHAT); amlodipine vs all active comparators excluding placebo (five studies); and amlodipine vs all other comparators including placebo (five studies). For each