Effect of Dose and Combination of Antihypertensives on Interindividual Blood Pressure Variability
A Systematic Review

Alastair John Stewart Webb, BMBCh; Peter Malcolm Rothwell, FMedSci

Background and Purpose—Recent studies have shown that visit-to-visit blood pressure variability is a powerful risk factor for stroke, is reduced by calcium channel blockers and diuretics, and increased by β-blockers. However, it is unknown whether these effects are dose-dependent and persist in combination with other drugs.

Methods—Cochrane and Medline databases were searched for systematic reviews and randomized controlled trials of antihypertensive drugs. Eligible trials randomized all patients to a combination of drug classes or different doses of the same drug. Baseline and follow-up data for mean (SD) systolic blood pressure (SBP) and diastolic blood pressure were extracted. Differences in interindividual variance (SD²) in blood pressure were expressed as a ratio (VR). Estimates were pooled by random-effects meta-analysis.

Results—Calcium channel blockers reduced interindividual variability in SBP when added to another agent (VR, 0.75; 95% CI, 0.64 to 0.87; P=0.0002; 12 trials; 1565 patients) with a smaller reduction with diuretics (VR, 0.85; 0.71 to 1.01; P=0.07; 17 trials; 3217 patients). Adding other agents to calcium channel blockers did not significantly affect SBP variability (VR, 1.06; 0.83 to 1.34; P=0.65; 12 trials; 1460 patients) despite a 5.8-mm Hg reduction in mean SBP. Randomization to a higher dose of calcium channel blockers reduced SBP variability (VR, 0.84; 0.74 to 0.94; P=0.004; 25 trials; 2179 patients), whereas randomization to a higher dose of β-blockers increased SBP variability (VR, 1.31; 1.01 to 1.69; P=0.034; 6 trials; 486 patients).

Conclusions—Effects of antihypertensive drugs on SBP variability are dose-dependent and persist when used in combinations. Use of a high dose of a calcium channel blocker alone or in combination with other agents is therefore likely to be particularly effective in prevention of stroke. (Stroke. 2011;42:2860-2865.)

Key Words: antihypertensive ■ blood pressure variability ■ combination ■ dose ■ stroke ■ systematic review

Recent reports demonstrated that patients with episodic hypertension have a high risk of stroke,1,2 that residual visit-to-visit variability in blood pressure (BP) on treatment has a poor prognosis despite good control of mean BP,1,3 and that benefits of some antihypertensives in the prevention of stroke are due partly to reduced variability in systolic BP (SBP).3,4 Variability in SBP is reduced by calcium channel blockers (CCBs), less so by diuretics, and increased by β-blockers (BBs), explaining class differences in effects on stroke risk in randomized controlled trials.3,4 However, these single-agent effects are difficult to relate to clinical practice in which, in accordance with current guidance, the majority of patients eventually end up on multiple agents for the control of mean SBP,5 and recent proposals have suggested combinations of drug classes at low doses as first-line treatment.6 However, we do not know whether antihypertensive drugs have the same magnitude of effects on variability in SBP when used in combinations and therefore whether they have the same effects on the risk of stroke. It is also important to better understand dose–response effects, including whether reductions in variability are likely to be found with proposed low-dose combination treatment. Although large randomized controlled trials including Anglo Scandinavian Cardiac Outcome Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)8 allowed add-on medications and dose titration, these nonrandomized interventions differed by both mean and variability in SBP. Therefore, these questions can only be addressed in trials with randomization to different fixed combinations or fixed doses. Therefore, we did a systematic review of such randomized controlled trials to determine how dose and combination treatment with antihypertensive drugs affect variability in SBP.

Methods
We searched the MEDLINE and Cochrane databases (1950 to Week 1, July 2009) using the following search terms: [meta(-)analysis] AND [antihypertensive agents OR blood-pressure lowering] as...
previously described. The reference lists of all identified reviews and corresponding web tables were subsequently searched. To improve inclusion of recent trials, we also searched MEDLINE from May 1, 2007, to May 1, 2010, with the terms: (1) [Trial] AND ["blood(-)pressure lowering" OR "antihypertensive"] AND ["combination"]; and (2) [Trial] AND ["blood(-)pressure lowering" OR "antihypertensive"] AND ["low(-)dose" OR "high(-)dose" OR "dose(-)response"].

For every trial fulfilling our inclusion criteria (Supplemental Table I, http://stroke.ahajournals.org) and randomizing patients to a fixed combination or fixed doses of the same drug, the main results article was reviewed. Mean (SD) BP at baseline and at all follow-up visits were extracted.

Within-trial differences between treatment groups in interindividual variance (SD²) in BP were expressed as the ratio of the variances of group SBP at each visit (VR) as a surrogate measure of intraindividual variability (Figure 1). As previously shown in 5 prospective cohorts, interindividual variance in SBP is dependent on both difference in mean SBP between individuals and intraindividual variability in SBP between different time points with 50% to 60% of interindividual variance in SBP at any specific time point being dependent on intraindividual variability between time points.1–4 Comparisons were pooled by random-effects meta-analysis using Mantel-Haenszel methods weighted by the inverse variance.4 Variance of VR was estimated from the natural logarithm of the 95% CI derived according to the F-distribution.3 The within-trial, between-group difference in the mean SBP or diastolic BP at follow-up was pooled by random-effects meta-analysis.

The analysis of dose–response included comparisons between different groups of patients randomized to different doses of the same drug (dose comparison) and between the same group of patients randomized to receive 1 dose of a drug and then receiving treatment with a higher dose of the same drug (dose escalation). For trials with >2 doses, each group was compared with the group receiving the highest dose of the drug. These within-trial comparisons were pooled across trials for each drug class. To assess the effect of drug classes on BP variability when used in combinations, only trials in which all patients were randomized to receive the allocated drugs in a specified regimen were used taking the group allocated to the highest dose of the combination and the SD at the follow-up closest to 1 year. Sensitivity analyses were performed in trials with <26 weeks of follow-up and, for all trials, taking the SD at median follow-up.

Comparisons analyzed were: (1) combination versus placebo (“AB versus Plac”); (2) combination versus monotherapy, including combinations containing the monotherapy treatment (“A versus AB”) and combinations not containing the monotherapy treatment (“A versus BC”); (3) combinations versus other combinations, including comparisons in which the 2 combinations did not share a drug class (“AB versus CD”) and where 1 drug class was the same in each combination (“AB versus AC”); and (4) trials in which SD was reported for a group of patients on a monotherapy treatment and after escalation to combination treatment for all patients (“A→AB”). These types of comparisons were then pooled for each specified drug class or drug combination as: (1) each drug class in combination compared with the combined agent alone (ie, all “A versus AB” and “A→AB” comparisons in which B is the assessed drug class); (2) each drug class alone compared with that drug class in combination with another (ie, all “A versus AB” + “A→AB” comparisons in which A is the assessed drug class); (3) each drug class in combination with any other agent versus any monotherapy or combination treatment not containing the drug class (ie, in which A is the drug: “AB versus XYZ” in which XYZ=”B,” “C,” “BC,” or “CD”); and (4) specific combinations of drug classes versus placebo, another combination, or a monotherapy regimen.

Monotherapy comparisons between each drug class and placebo are presented as calculated in the previous meta-analysis,4 including only trials in which patients were taken off all previous antihypertensives and no additional medications were allowed during the trial. Analyses were performed in SPSS Version 14.0 or Microsoft Excel 2007.
We identified 255 systematic reviews and meta-analyses, of which 68 were duplicate publications or reviewed trials in excluded patient groups. The remaining 187 meta-analyses generated 1858 citations to independent trials, resulting in 1372 eligible trials as described previously.4 Of these 1372 trials, 910 Phase 2 trials (71.2%) and 73 Phase 3 trials (77.7%) did not report the mean (SD) SBP or diastolic BP at baseline and follow-up. Of the remaining 389 trials, 38 randomized all patients in at least 1 group to a combination of drug classes, whereas 31 randomized patients to different fixed doses of the same agent (21 dose comparison and 10 dose escalation studies; w15, w23, w26, w29, w39 to w64). The additional searches for combinations or doses generated 686 and 239 abstracts, respectively, of which 108 and 22 were independent studies, which 1 drug (B) was added to another agent compared with that agent alone (Figure 3A). There was a highly significant reduction in VR when adding a BB despite a similar reduction in SBP with BBs, although neither comparison was independently significant (VR for high dose versus low dose: CCBs, 0.89; 0.71 to 1.12; BB, 1.22; 0.83 to 1.77). There were no such trials using diuretics or angiotensin receptor blockers.

Across 68 combination therapy trials, 15 comparison were between different specified combinations (3 “A versus BB,” 12 “A versus AC”), insufficient to draw conclusions about the effects of specific combinations in direct comparison. There were 22 “A versus AB” and “A→AB” comparisons in which 1 drug (B) was added to another agent compared with that agent alone (Figure 3A). There was a highly significant reduction in VR when adding a CCB to another drug class for a relatively small reduction in mean SBP and no significant reduction in VR when adding a BB despite a similar reduction in SBP. The overall pattern of drug class effects was the same in drug versus placebo comparisons in our previous meta-analysis (Figure 3B), and was unaltered when the analysis was limited to trials with <26 weeks of follow-up (CCBs: VR, 0.78; 0.68 to 0.95; P=0.017; BB, 1.06; 0.58 to 1.93; P=0.085). The magnitude of reduction in VR for 3 trials in which a CCB was added to a BB was similar to adding a CCB to any agent (VR, 0.76; 0.45 to 1.27; 124 patients), whereas 4 trials in which a BB was added to a CCB had no effect on VR (VR, 0.97; 0.44 to 2.11; 193 patients).

For the analysis of the difference in VR for each drug class as monotherapy compared with that class in combination with another (“A versus AB” or “A→AB” in which A is the class in question), there was no change in VR when adding another drug to a CCB, although mean SBP was reduced, whereas adding another drug to an angiotensin-converting enzyme inhibitor significantly reduced VR (CCBs: VR, 1.06; 0.83 to 1.34; P=0.6469; mean difference SBP=−5.8 mm Hg, 1460 patients, 12 comparisons; angiotensin-converting enzyme inhibitor: VR, 0.72; 0.61 to 0.86; P=0.0003, difference SBP=−4.7 mm Hg). Adding another class to BBs, diuretics, or angiotensin receptor blockers nonsignificantly reduced VR.
(BBs: VR, 0.81; 0.53 to 1.25; diuretics: VR, 0.83; 0.59 to 1.16; angiotensin receptor blockers: VR, 0.93; 0.80 to 1.07). For “AB versus XYZ” comparisons, there was a significant reduction in VR for combinations containing a CCB compared with treatment regimes not containing a CCB with a smaller reduction in VR for combinations containing a diuretic compared with regimens not containing a diuretic, and no significant differences with other drug classes (CCB: VR, 0.79; 0.66 to 0.95; 2564 patients; 20 comparisons; P=0.012, mean difference SBP=−3.3 mm Hg; diuretics: VR, 0.85; 0.73 to 0.99; 5263 patients; 31 comparisons; P=0.03, mean difference SBP=−4.4 mm Hg).

There were 12 comparisons of specific combinations with placebo; however, there were only sufficient trials to assess the addition of a CCB or a diuretic to an angiotensin-converting enzyme inhibitor. These demonstrated a reduction in VR (Figure 4) for the addition of either drug to an angiotensin-converting enzyme inhibitor. Although the pooled reduction in VR with CCB+angiotensin-converting enzyme inhibitor versus placebo was less than CCB versus placebo, this difference resulted from 1 trial that used only 2.5 mg amlodipine in combination with 10 mg benazepril. Excluding this low-dose trial, the reduction in VR is equivalent to that seen with CCB versus placebo (VR, 0.70; 0.58 to 0.86; P=0.0003; n=769).

**Discussion**

We recently showed that increased visit-to-visit variability in SBP is associated with an increased risk of stroke, independently of mean BP,1,2 that visit-to-visit variability in SBP is reduced by CCBs and increased by BBs, and that these effects correlate with class differences in effectiveness in preventing stroke in randomized controlled trials.3,4 However, a previous meta-analysis suggested that low-dose combinations of anti-

**Figure 3.** Pooled estimates of within-trial comparisons of the effect of each drug class on variability in systolic blood pressure at follow-up. A, Comparison of each class of drug in combination with another drug class versus the combination drug alone. B, Comparison of each class of drug as monotherapy versus placebo. B are data from our previous meta-analysis4 for trials in which no other antihypertensive drugs were allowed during the trial. Estimates are pooled by random-effects meta-analysis with 95% CIs. CCB indicates calcium channel blockers; DD, diuretics; ARB, angiotensin receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; BB, β-blockers; Het, heterogeneity; SBP, difference in mean SBP; Comp, comparison; SBP, systolic blood pressure.

**Figure 4.** Pooled estimates of within-trial comparisons of the effect on variability in systolic blood pressure at follow-up of calcium channel blockers or diuretics as monotherapy or in combination with an ACEI compared with placebo. Monotherapy comparisons are data from our previous meta-analysis,5 for trials in which no other antihypertensive drugs were allowed during the trial. Estimates are pooled by random-effects meta-analysis with 95% CIs. CCB indicates calcium channel blockers; DD, diuretics; ACEI, angiotensin-converting enzyme inhibitor; Het, heterogeneity; SBP, difference in mean SBP; Comp, comparison; SBP, systolic blood pressure.
hypertensive drugs had an equivalent impact on mean BP compared with higher doses of monotherapies6 and would therefore result in an equal reduction in the risk of stroke. Another meta-analysis from the same group7 suggested only minimal differences between antihypertensive drug classes. The majority of hypertensive patients currently escalate to combination treatment, but these studies have led to proposals to initiate antihypertensive treatment with low-dose combinations. Therefore, we determined how combining drug classes affects visit-to-visit variability in SBP and whether effects on variability are diminished with low-dose treatment.

This meta-analysis showed that higher doses of CCBs reduce BP variability more than lower doses, and higher doses of BBs increase BP variability. Thus, combinations containing a low dose of BB will have less adverse effects on variability in SBP and the associated risk of stroke, but low doses of CCBs will be less effective in reducing variability in BP and hence their use would be anticipated to lead to less reduction in the risk of stroke.

We also showed that drug class effects on variability in SBP persisted when drugs were used in combination. In particular, adding a CCB or diuretic to another antihypertensive drug reduced variability in SBP to the same extent as seen with monotherapy versus placebo. In contrast, adding an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to another class had no significant impact on variability in SBP. Addition of a CCB to a BB had an equivalent effect compared with addition of a CCB to any other agent, whereas addition of a BB to a CCB did not increase VR, although there were too few trials to draw definitive conclusions about BBs. This suggests that the use of CCBs may partly nullify the detrimental impact of BBs on variability in SBP. For other classes, the effect of each class in combination was the same as when used as monotherapy, suggesting the mechanism of action of CCBs on variability in SBP is either dominant or independent of the mechanism of action of diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers.

The main limitations of this review result from the small number of trials randomizing patients to specific drug combinations and reporting measures of BP variability relative to the large number of possible comparisons. First, by pooling different combinations of classes, the results could be confounded by the frequency with which each class is combined with or compared with another. However, this could not result in bias in the main analysis of “A versus AB” in which the combination drug is balanced between groups. Second, there were insufficient trials to measure the dose–response of agents when used as part of a combination. However, given the equivalent effect of each class when used in combination compared with monotherapy, extrapolating the effect of dose in monotherapy comparisons to the effect of dose in combinations is valid. Third, the small number of trials means that we were unable to directly assess the impact of combinations of classes in use for specific indications. For example, there are no trials using the theoretically ideal combination (in terms of reducing variability in SBP) of a CCB and a diuretic, and so we were unable to assess whether reduction in BP variability with these 2 classes is additive, synergistic, or redundant. Felodipine Event Reduction (FEVER)8 randomized patients to hydrochlorothiazide versus hydrochlorothiazide plus felodipine, but there was only a small additional reduction in BP variation in the CCB group (VR, 0.90; 0.85 to 0.96) due to the low dose of felodipine (5 mg) used in FEVER. In addition, higher doses of hydrochlorothiazide were used in the monotherapy arm than the combination arm, reducing any differences in variability in SBP between the groups. Fourth, these results are not explicable by more patients responding to regimens with a lower variability: the magnitude of difference in VR (a 25% reduction with CCBs) would require a greater proportion of responders to CCBs compared with other classes than is usually seen, including in ASCOT-BPLA; large differences in the proportion of patients responding would result in a greater reduction in mean SBP. We would not expect a greater variability with a higher dose of BBs versus reduced variability with a higher dose of CCBs, especially given the similar reductions in mean SBP. Finally, this analysis is by necessity a post hoc analysis because no randomized controlled trials prospectively assessed the effect of regimens on SBP variability or cardiovascular outcomes.

In relation to the place of combination therapy with CCBs for stroke prevention in current clinical practice, the combination of perindopril and indapamide is widely used in secondary stroke prevention and in the elderly following the results of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)9 and Hypertension in the Very Elderly (HYVET)10 trials. Our analyses suggest that addition of a CCB to this combination will further reduce the risk of future stroke, but there were no eligible trials directly addressing this possibility. In addition, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are recommended in patients with renal impairment or diabetic nephropathy. Variability in SBP and stroke risk were both increased by randomization to an angiotensin-converting enzyme inhibitor compared with other antihypertensive drug classes in our previous meta-analysis,4 but this meta-analysis suggests that the possible detrimental effect of these drugs on variability in SBP may be offset by combination use with CCBs, allowing their use for these indications without causing harm. This may provide a potential explanation for the improved renal outcomes in the angiotensin-converting enzyme inhibitor+CCB group in the Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial.11 More research is required to identify ideal combinations and doses of drugs for the prevention of stroke in specific patient groups with particular reference to effects on variability in BP.

Conclusions
The reduction in variability in SBP seen with calcium channel blockers and diuretics when used as monotherapy is maintained when the drugs are used in combination with other classes. However, the effects of CCBs and BBs on variability in BP depend on dose with important implications for the effectiveness of low-dose combination treatment in preventing stroke. Use of a high-dose of a CCB alone or in
Combination with other agents is likely to be particularly effective in prevention of stroke.

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**Disclosures**
None.

**References**
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SUPPLEMENTAL DATA

EFFECT OF DOSE AND COMBINATION OF ANTIHYPERTENSIVES ON INTER-
INDIVIDUAL BLOOD PRESSURE VARIABILITY: A SYSTEMATIC REVIEW

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**Webtable 1 – Characteristics of included trials.**

**Inclusion Criteria**
- Controlled trials, group allocation by randomisation, minimisation or similar
- Reported in peer-reviewed journal available in the British Library.
- >2 weeks of follow-up.
- Any language.
- Reports number of patients and mean and standard deviation at both baseline and follow-up of either systolic or diastolic blood pressure.
- Trials must contain either: one group wherein all patients are randomised to a combination of drug classes or two groups randomised to different doses of the same drug.

**Exclusion Criteria**
- Trials requiring a recent acute cardiovascular event (within 3 months of a stroke, myocardial infarction or chest pain requiring intervention)
- Trials requiring patients with: active left ventricular failure (symptomatic or ejection fraction <40%), portal hypertension, severe liver disease, pulmonary hypertension, dialysis dependent renal failure, major life-limiting disease or disease causing significant functional impairment (excluding stroke more than 3 months prior to randomisation).

**Data Collection**
- Trial validity: Randomisation, blinding, intention-to-treat analysis, washout of prior medications.
- Inclusion/exclusion criteria
- Demographic characteristics: Number of patients, age, gender, ethnicity and disease characteristics.
- Treatment: Dose, frequency and duration of treatment with trial agents, pre-existing and maintained medications affecting blood pressure and any add-on antihypertensives during the trial.
- Results: The baseline and follow-up measures of systolic and diastolic blood pressure and the associated standard deviation at each timepoint recorded in the trial, if reported numerically.
Web-figure 1. Standard deviation at follow-up plotted against logarithm of group size for all drug groups allocated CCBs or BBs. The distributions are symmetrical without clear reporting bias and the large trials accurately reflect the average of smaller trials.


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Key Words: antihypertensive ■ blood pressure variability ■ dose ■ stroke ■ systematic review
Figure 2. Pooled estimates of the effect of within-trial comparisons of higher versus lower doses of the same drug on variability in systolic blood pressure at follow-up according to drug class. Estimates of variability in SBP are expressed as the ratio of variance (VR), VR and difference in mean SBP are pooled by random-effects meta-analysis with 95% CIs. CCB indicates calcium channel blockers; DD, diuretics; ARB, angiotensin receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; BB, β-blockers; Het, heterogeneity; SBP, difference in mean SBP; Comp, comparison; SBP, systolic blood pressure.

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Figure 3. Pooled estimates of within-trial comparisons of the effect of each drug class on variability in systolic blood pressure at follow-up. A, Comparison of each class of drug in combination with another drug class versus the combination drug alone. B, Comparison of each class of drug as monotherapy versus placebo. B are data from our previous meta-analysis for trials in which no other antihypertensive drugs were allowed during the trial. Estimates are pooled by random-effects meta-analysis with 95% CIs. CCB indicates calcium channel blockers; DD, diuretics; ARB, angiotensin receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; BB, β-blockers; Het, heterogeneity; SBP, difference in mean SBP; Comp, comparison; SBP, systolic blood pressure.

B

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Figure 4. Pooled estimates of within-trial comparisons of the effect on variability in systolic blood pressure at follow-up of calcium channel blockers or diuretics as monotherapy or in combination with an ACEI compared with placebo. Monotherapy comparisons are data from our previous meta-analysis for trials in which no other antihypertensive drugs were allowed during the trial. Estimates are pooled by random-effects meta-analysis with 95% CIs. CCB indicates calcium channel blockers; DD, diuretics; ACEI, angiotensin-converting enzyme inhibitor; Het, heterogeneity; SBP, difference in mean SBP; Comp, comparison; SBP, systolic blood pressure.
降圧薬の用量および併用が個体間血圧変動へ及ぼす影響
— 系統的レビュー —

Effect of Dose and Combination of Antihypertensives on Interindividual Blood Pressure Variability — A Systematic Review

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Abstract

降圧薬の用量および併用が個体間血圧変動へ及ぼす影響
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各クラスの薬剤が追跡調査中に収縮期血圧に及ぼす効果に関する試験数比較の結果示す。A. 各クラスの薬剤の他のクラスとの併用と併用薬単独投与との比較。B. 各クラスの薬剤の単独投与とプラセボとの比較。

B は試験中の他の降圧薬の使用を避めた試験について我々が過去に実施したメタアナリシスのデータで、推定値は変量効果メタアナリシスにより統合し、95% CI を示した。CBB：カルシウムチャネル遮断薬、DD：利尿薬、ARB：アングイオテンシン変換酵素阻害薬、ACEI：アングリオテンシン変換酵素阻害薬、BB：β遮断薬、Het：不均一性、SBP：平均収縮期血圧の差。Comp：比較。