Blood Pressure Variability and Risk of New-Onset Atrial Fibrillation
A Systematic Review of Randomized Trials of Antihypertensive Drugs

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Background and Purpose—Increased visit-to-visit variability in blood pressure (BP) is a powerful risk factor for stroke, but the mechanism is uncertain. We hypothesized that BP variability might affect the risk of new atrial fibrillation (AF).

Methods—We did a systematic review of large randomized controlled trials reporting new-onset AF by treatment allocation, excluding studies in heart failure and acute myocardial infarction. Estimates of the risk of new AF by treatment allocation were related to effects of treatment on group variability in BP.

Results—Of 94 eligible randomized controlled trials, 14 reported rates of new AF. Although there was considerable heterogeneity between trials in effects of treatment on variability in blood pressure (BP) (P<0.0001), lower variance ratio was unrelated to new-onset AF either on meta-analysis (OR=1.02; 95% CI 0.90 to 1.15; 125,878 patients; 13 comparisons) or on metaregression (log OR versus log variance ratio of systolic blood pressure \( r^2 = 0.109, P = 0.270 \)). Angiotensin receptor blockers tended to reduce new-onset AF (OR 0.85; 95% CI 0.71 to 1.01; \( P = 0.067 \); 4 trials; 47,482 patients) with significant reductions in 2 individual trials but had no consistent reduction on variability in BP.

Conclusions—Effects of randomized treatment on variability in BP are unrelated to risk of new-onset AF, suggesting that other mechanisms account for the link between variability and stroke risk. However, a lower incidence of AF in patients randomized to angiotensin receptor blockers may explain reductions in stroke risk in some trials. (Stroke. 2010;41:2091-2093.)

Key Words: atrial fibrillation ■ cardiac embolism ■ cerebrovascular accident ■ hypertension ■ prevention

Increased intradividual visit-to-visit variability in systolic blood pressure (SBP) is associated with an increased risk of stroke, independent of mean SBP,\(^1,2\) and antihypertensive drug class effects on variability in blood pressure (BP) correlate with effects on stroke risk in randomized controlled trials (RCTs).\(^3,4\) However, the mechanism of the association between BP variability and risk of stroke is uncertain. We hypothesized that BP variability might affect the risk of development of new-onset atrial fibrillation (AF). BP variability is a risk factor for heart failure,\(^2\) but any association with risk of AF is uncertain. We showed previously that effects of antihypertensive drugs on group variation in SBP in RCTs are a surrogate for their effects on intradividual variability in SBP.\(^1,3,4\) We therefore did a systematic review of RCTs of antihypertensive drugs to determine whether effects of randomized treatment on variability in BP correlated with effects on risk of new-onset AF.

Methods

Medline was searched with the terms (“trial”) AND (“blood[-]pressure lowering” OR “antihypertensive”) AND (“atrial fibrillation”). The resulting citations and abstracts were reviewed (A.J.S.W.) and any potentially eligible report was reviewed in full. All RCTs of BP-lowering agents randomizing >200 patients for >1 year that reported rates of new-onset AF by treatment group were included. Trials were excluded if they were performed specifically in patients with heart failure, liver disease, pulmonary hypertension, dialysis-dependent renal failure, pregnancy or history of AF, or within 3 months of an acute vascular event. Primary reports of 94 RCTs from our previous meta-analysis\(^4\) were also reviewed.

Mean (SD) BP and incidence of AF at baseline and at all follow-up visits were extracted. Treatment group differences in BP variation were expressed as the ratio of the variances\(^4\) (variance ratio \( \text{VR} = \text{SD}^2 / \text{SD}^2 \) closest to 1 year of follow-up. Differences in new AF over the entire follow-up were compared by OR. Natural logarithms of VR and ORs were pooled by variance-weighted Mantel-Haenszel random-effects meta-analysis. Variance of VR was estimated from its 95% CI derived from the F-distribution. For all trials, we pooled the OR for new AF in the group with the lower versus higher SD SBP and correlated log(VR) with log(OR) for new AF weighted by the inverse variance of OR for both SBP and diastolic BP. We also determined drug class effects on risk of new AF. Analyses were done with Microsoft Excel 2007 or SPSS Version 14.0.

Results

The initial search generated 401 citations with 36 eligible RCTs reviewed in full, of which 7 reported new-onset AF. An additional 7 primary reports of trials identified in the previous meta-analysis\(^4\) also reported new AF, giving 14 trials in total. SD SBP or SD diastolic BP at ≥1 follow-ups was available.
for 9 of these trials. Two trials had 3 treatment arms, resulting in 13 comparisons between groups reporting both VR and OR for new-onset AF.5–13

There was significant heterogeneity between trials in effects of treatment on VR ($P<0.0001$; Figure 1) and in effects on new-onset AF ($P=0.0017$). However, lower VR was unrelated to new-onset AF either on meta-analysis (group with lower versus higher SD SBP; OR = 1.02; 95% CI 0.90 to 1.15; 125,878 patients; 13 comparisons; Figure 1) or on metaregression (log OR versus log VR SBP $r^2=0.109, P=0.270$; Figure 2). Differences in mean SBP during follow-up were also unrelated to effects on new AF (meta-analysis OR 0.98; 0.87 to 1.11; metaregression log OR versus log VR SBP $r^2=0.044, P=0.42$). Results were similar for VR diastolic BP.

New-onset AF was significantly reduced by randomization to an angiotensin receptor blocker in 2 trials (versus a β-blocker/calcium channel blocker)6,7 with a trend in a pooled analysis of all angiotensin receptor blockers versus other drug comparisons (OR = 0.85; 0.71 to 1.01; $P=0.067$; 4 trials; 47,482 patients), but there were no parallel effects of angiotensin receptor blockers on VR SBP or diastolic BP. There were no other drug class effects in any individual trial or in pooled analyses.

Figure 1. Within-trial differences in risk of new-onset AF comparing the lower SD SBP group with higher SD SBP. VR indicates variance ratio between groups; SBP, difference in SBP; DD, diuretics; Plac, placebo; AB, α-blocker; CCB, calcium-channel blocker; ACE, angiotensin-converting enzyme blocker; ARB, angiotensin receptor blocker; BB, β-blocker. *Weighting adjusted for multiple treatment arms.

**Discussion**

We found no association between effects of antihypertensive drugs on group variability in BP and effects on new-onset AF. In addition, calcium channel blockers and non-loop diuretics, the drug classes that reduce variability in BP, did not reduce risk of new AF. New AF was reduced by angiotensin receptor blockers in 2 trials, but angiotensin receptor blockers have little, if any, effect on variability in BP. Taken together, these results suggest that other mechanisms account for the link between BP variability and stroke risk.

The main shortcoming of our article is that only a few trials reported both rates of new-onset AF and group variation in BP during follow-up. However, given that most of the individual trials were large enough to determine effects on variability in BP and effects on new AF reliably, the lack of any association between effects on variability and effects on AF is convincing nevertheless.

The lack of any association between effects on variability and effects on AF induced by antihypertensive drugs in trials does not completely exclude the possibility of an association between variability in BP and risk of AF in general population cohorts, but it suggests that major confounding is unlikely.
Disclosures

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References

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The article entitled, “Blood Pressure Variability and Risk of New-Onset Atrial Fibrillation: A Systematic Review of Randomized Trials of Antihypertensive Drugs” by Webb and Rothwell, which published the September 2010 issue of the journal (Stroke, 2010;41:2091–2093), should have included the below disclosure information:

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Correction

The article entitled, “Blood Pressure Variability and Risk of New-Onset Atrial Fibrillation: A Systematic Review of Randomized Trials of Antihypertensive Drugs” by Webb and Rothwell, which published the September 2010 issue of Stroke, should have included the below disclosure information:

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