Medium-Term Variability of Blood Pressure and Potential Underdiagnosis of Hypertension in Patients With Previous Transient Ischemic Attack or Minor Stroke

Robert L. Cuffe, MSc; Sally C. Howard, DPhil; Ale Algra, PhD; Charles P. Warlow, FRCP; Peter M. Rothwell, FRCP

Background and Purpose—Blood pressure (BP) is a major risk factor for stroke. However, the variability of systolic and diastolic BP (SBP and DBP) means that single measurements do not provide a reliable measure of usual BP. Although 24-hour ambulatory BP monitoring can correct for the effects of short-term variation, there is also important medium-term variability. The extent of medium-term variability in BP is most marked in patients with a previous transient ischemic attack (TIA) or stroke. We studied the potential impact of this variability on the likely recognition of hypertension.

Methods—We analyzed multiple repeated measurements of BP in 3 large cohorts with a TIA or minor stroke: the UK-TIA trial (n=2098), the Dutch TIA trial (n=2953), and the European Carotid Surgery Trial (ECST; n=2646). Regression dilution ratios and coefficients of variation were calculated for SBP and DBP from baseline and repeated measurements during the subsequent 12 months. Categorization based on single baseline measurements was also compared with categorization based on the subsequent “usual” BP.

Results—The correlation between measurements of BP at baseline and 3 to 5 months later was poor (R² from 0.17 to 0.31 for SBP and from 0.10 to 0.20 for DBP). Categorization of patients by baseline values resulted in substantial misclassification in relation to usual BP. For example, of patients with an SBP <140 mm Hg at baseline, the percentage with a usual SBP ≥140 mm Hg was 31.6% in the UK-TIA trial, 48.2% in the Dutch TIA trial, and 57.7% in the ECST. At least 3 consecutive measurements of SBP <120 mm Hg were required to be >90% certain that subsequent usual SBP would not be ≥140 mm Hg.

Conclusions—Given the greater medium-term variability of BP in patients with a previous TIA or stroke than in the general population, single measurements of “normal” or “low” BP will substantially underestimate the true prevalence of hypertension. (Stroke. 2006;37:2776-2783.)

Key Words: hypertension ■ prevention ■ risk factors ■ stroke

Blood pressure (BP), particularly systolic blood pressure (SBP), is the most powerful risk factor for ischemic stroke.1-3 BP lowering is highly effective in preventing stroke in both primary prevention4 and in the medium and long term after a transient ischemic attack (TIA) or stroke.5 In the secondary prevention setting, the PROGRESS Trial showed that the relative benefit from BP lowering was independent of baseline BP,5 which is consistent with previous observational epidemiological studies.6 It is therefore recommended that most patients with a previous TIA or stroke begin BP-lowering medication, irrespective of their baseline BP.5,7 However, as in the primary prevention setting,8 there remains widespread undertreatment with BP-lowering medication after TIA and stroke.9,10 One possible reason for this underuse of BP-lowering medication after TIA and stroke is residual uncertainty among clinicians about the need for treatment in patients with “normal” SBPs, despite the findings of the PROGRESS Trial. It is possible that patients and clinicians are being falsely reassured by “normal” levels of SBP after TIA or stroke, particularly if that assessment is based on only 1 or 2 measurements. We have shown that the variability in BP over months and years in patients with a previous TIA or stroke is much greater than that seen in the general population.11 Variability of BP measurements over time within individuals is a widely recognized phenomenon with important implications for the diagnosis of hypertension and for estimating risk relations.12 Screening for hypertension can be subject to substantial misclassification error if based on only a single measurement of BP, and estimates of the prevalence of hypertension can be highly biased if appropriate correction for within-person variability is not made.13,14 Measurements obtained from 24-hour amb-

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2776
Bulotary BP monitoring can reduce the effects of short-term (daily) variation, but there are also important medium-term (within weeks or months) components of variability in patients with a previous TIA or stroke, possibly related to age or more widespread vascular pathology.

Much of the previous work on misclassification of individuals in relation to measured BP has concentrated on "white coat hypertension" and the extent to which 1-off high measurement of BP can overdiagnose hypertension, but there has been less work on the extent to which 1-off measurement of "normal" BP can lead to the underdiagnosis of hypertension. However, given the results of the PROGRESS Trial, the latter question is of clinical relevance in patients with TIA or stroke. To determine the extent to which a single measurement of BP at the lower end of the range might underestimate usual BP in patients with a previous TIA or stroke, we analyzed medium-term variability (defined as variability over weeks and months) by using repeated measurements of SBP and diastolic blood pressure (DBP) in 3
large trial populations of patients presenting with a TIA or minor ischemic stroke.20–22 These patients were older than those in population-based studies of intraindividual variability,1–3,23 and all had established cerebrovascular disease.

**Subjects and Methods**

**Study Populations**

The UK-TIA trial20 was a trial of long-term treatment with aspirin (1200 mg versus 300 mg versus placebo) in 2435 patients with a TIA or minor ischemic stroke. After randomization, patients were seen every 4 months until the scheduled end of the trial, death, or emigration. The Dutch TIA trial21 was a factorial randomized, controlled trial involving 2 treatment comparisons in 3150 patients with a TIA or minor ischemic stroke in which 3131 patients were randomized to aspirin 30 mg versus 283 mg aspirin, and 1473 patients were randomized to atenolol 50 mg versus placebo. After randomization, patients were seen every 4 months. The European Carotid Surgery Trial (ECST)22 was a randomized, controlled trial of carotid endarterectomy versus best medical treatment alone in 3018 patients with recently symptomatic carotid stenosis. All patients were followed up every 4 months. The UK-TIA trial before follow-up was available, were excluded from the analyses, because no measure of variability could be obtained for these patients. BP measurements recorded subsequent to any stroke or myocardial infarction on follow-up were not used in the analyses to avoid any bias from changes in BP induced by these events.

Agreement between baseline and second measurements of SBP and DBP as continuous variables was assessed with the intraclass correlation coefficient (ICC). Variability in multiple, repeated BP measurements within individuals during follow-up was also assessed with the standard deviation (SD) and the coefficient of variation (CV) of the measurements. CV has the advantage that it is standardized for the absolute level of BP, representing the SD as a percent of the mean. The extent of misclassification resulting from use of a different group.

**Statistical Analysis**

For each individual, baseline and all available repeated measurements of both SBP and DBP were used in the analysis. Patients with only a baseline measurement of BP, because of death or termination of the trial before follow-up was available, were excluded from the analyses, because no measure of variability could be obtained for these patients. BP measurements recorded subsequent to any stroke or myocardial infarction on follow-up were not used in the analyses to avoid any bias from changes in BP induced by these events.

In the first, we divided patients into groups on the basis of DBP (<80, 80 to 90, ≥90 mm Hg) and SBP (<140, 140 to 159, ≥160 mm Hg) twice: once on the basis of baseline measurements and once on the basis of underlying, or “usual,” BP, estimated by the mean of all repeated measurements within 12 months (ie, 3 follow-up measurements in the UK-TIA and Dutch TIA trials and 2 measurements in the ECST). We then calculated, for each baseline group, the percentage of patients whose usual measurement fell into a single baseline measurement was assessed in the following 2 analyses.

In the second, we divided patients into groups on the basis of DBP (<80, 81 to 90, ≥90 mm Hg) and SBP (<140, 140 to 159, ≥160 mm Hg) twice: once on the basis of baseline measurements and once on the basis of underlying, or “usual,” BP, estimated by the mean of all repeated measurements within 12 months (ie, 3 follow-up measurements in the UK-TIA and Dutch TIA trials and 2 measurements in the ECST). We then calculated, for each baseline group, the percentage of patients whose usual measurement fell into a single baseline measurement was assessed in the following 2 analyses.
In the second method, patients were also classified into smaller 10-mm Hg bands of SBP and 5-mm Hg bands of DBP on the basis of their baseline reading. The proportion of patients in each band whose usual BP during the first year of follow-up was greater than a given threshold (eg, a mean SBP of 140 mm Hg) diminishes with increasing numbers of consecutive measurements of “normal” SBP, we restricted our analysis to patients with the first n consecutive measurements of “normal” SBP, and those not randomized to atenolol, the number with BP measurements at baseline and at the first point of follow-up was 2269 (92.8%). No treatment allocation effect differences were found in the UK-TIA trial, so analyses were performed for all treatment groups combined.

### Results

The number of patients with BP measurements at baseline and at the first point of follow-up was 2098 (86.2%) in the UK-TIA trial, 2953 (93.7%) in the Dutch TIA trial, and 2646 (87.7%) in the ECST. Mean (SD) ages were 60.1 (8.9), 65.0 (10.0), and 62.3 (8.1) years, respectively; the proportions of men were 73%, 65%, and 72%, respectively. Mean (SD) SBP levels at baseline were 150.8 (25.1), 157.8 (26.2), and 150.3 (21.8) mm Hg, respectively, and mean (SD) DBPs were 88.0 (11.8), 90.8 (13.2), and 86.1 (11.3) mm Hg, respectively. In the UK-TIA trial, there were 1732 (71%) patients with follow-up measurements at 4, 8, and 12 months; in the Dutch TIA trial, there were 2603 (83%) patients with measurements at 4, 9, and 13 months; and in ECST, there were 2318 (77%) patients with measurements at 5 and 14 months after randomization.

Initial analyses were performed to test for heterogeneity of agreement between baseline and second measurements between the treatment groups in each trial; eg, between the surgical and medical arms of the ECST. It was particularly important to compare the ICC between patients randomized to receive atenolol (n=686) and those not randomized to atenolol (n=700) in the Dutch-TIA trial. ICCs tended to be lower for those randomized to atenolol: for SBP, 0.38; 95% CI, 0.31 to 0.44; and for DBP, 0.28; 95% CI, 0.20 to 0.34 versus no atenolol; SBP, 0.41; 95% CI, 0.35 to 0.47; and DBP, 0.38; 95% CI, 0.31 to 0.44 (P=0.51 for SBP, P=0.04 for DBP). Those patients randomized to receive atenolol were therefore excluded from subsequent analyses. Of the 2445 patients in the Dutch TIA trial who were not randomized to atenolol, the number with BP measurements at baseline and at the first point of follow-up was 2269 (92.8%). No treatment allocation effect differences were found in the UK-TIA trial or the ECST, so analyses were performed for all treatment groups combined.

### Table 2. ICCs for DBP (R) Between Baseline and Second Measurements by Patient Characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>UK-TIA</th>
<th>Dutch TIA</th>
<th>ECST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>R (CI)</td>
<td>P</td>
</tr>
<tr>
<td>Total</td>
<td>2098</td>
<td>0.45 (0.41–0.48)</td>
<td>. . .</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1537</td>
<td>0.45 (0.41–0.49)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>561</td>
<td>0.45 (0.38–0.51)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;64 y</td>
<td>1337</td>
<td>0.44 (0.40–0.49)</td>
<td></td>
</tr>
<tr>
<td>≥64 y</td>
<td>761</td>
<td>0.44 (0.38–0.49)</td>
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</tr>
<tr>
<td>Days since presenting event</td>
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<tr>
<td>&lt;30</td>
<td>1146</td>
<td>0.46 (0.41–0.50)</td>
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<tr>
<td>31–90</td>
<td>789</td>
<td>0.43 (0.37–0.48)</td>
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<tr>
<td>≥90</td>
<td>119</td>
<td>0.41 (0.25–0.55)</td>
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<td>Presenting event</td>
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<tr>
<td>Stroke</td>
<td>405</td>
<td>0.45 (0.37–0.53)</td>
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<tr>
<td>TIA</td>
<td>1354</td>
<td>0.45 (0.41–0.49)</td>
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<td>567</td>
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<tr>
<td>No</td>
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<tr>
<td>Yes</td>
<td>72</td>
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<tr>
<td>No</td>
<td>2026</td>
<td>0.45 (0.41–0.48)</td>
<td></td>
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<tr>
<td>Previous myocardial infarction</td>
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<tr>
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<td>210</td>
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<td>No</td>
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<td>Smoking</td>
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<tr>
<td>No</td>
<td>1003</td>
<td>0.44 (0.39–0.49)</td>
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Figure 1 shows plots of second measurements against baseline measurements for SBP and DBP in the 3 trial populations. The patterns in each trial are consistent, with a large amount of scatter for both SBP and DBP. The $R^2$ values (given by the squared ICCs) ranged from 0.17 to 0.31 for SBP and from 0.10 to 0.20 for DBP. Plots that omitted patients who had a myocardial infarction between their baseline and first follow-up reading showed the same spread of values. Tables 1 and 2 show how the ICC between the baseline and second measurements varied according to patient characteristics. In each study, the largest difference was between patients who were on antihypertensive treatment at baseline versus those who were not, with smaller ICCs observed among those on treatment. There were no differences between men and women and little suggestion of an effect of age. Smaller ICCs were observed in older patients in ECST, but this trend was not evident in either the UK-TIA trial or the Dutch TIA trial. There was a consistent tendency for smaller ICCs in patients who had presented with a stroke than in those with a TIA. However, there was no evidence that the ICC was influenced by the time since the presenting event, smoking, or diabetes.

Overall intraindividual variation in measurements of BP during the first year of follow-up (including the baseline measurement) was assessed as the SD and CV. The average intraindividual SDs for SBP were 13.6 in the UK-TIA trial, 15.0 in the Dutch TIA trial, and 13.9 mm Hg in the ECST. For DBP, the average intraindividual SDs were 7.6, 7.8, and 7.4 mm Hg, respectively. Supplemental Table I (available online at http://stroke.ahajournals.org) shows the overall mean CV for each trial, together with the mean CV by various patient characteristics. In each trial, the CVs for SBP were significantly higher in patients who were on antihypertensive treatment at baseline. In the UK-TIA trial and the ECST, CVs for DBP were also significantly higher in patients who were on antihypertensive treatment. In women, CVs for SBP were significantly higher than in men, but not for DBP. No other patient characteristics had significant effects on the CVs.

The effects of variation in measured BP during follow-up on the classification of SBP and DBP are shown in Figures 2 and 3, which show the classification of patients according to their average, or “usual,” measurement, after categorization by baseline measurement. There was substantial movement between categories, a finding that is consistent across all 3 trials. In Figure 2, for example, of patients with an SBP $\geq$140 mm Hg at baseline, the percentage with usual SBP $\leq$140 mm Hg was 32% in the UK-TIA trial, 48% in the Dutch TIA trial, and 58% in the ECST. Of patients with a baseline DBP $<80$ mm Hg, the percentages with usual DBP $\geq$80 mm Hg were 56%, 62%, and 71%, respectively. Figure 3 shows the same analysis broken down into 10-mm Hg bands of both baseline and usual BP.

Figure 4 shows the extent to which the potential for underdiagnosis of systolic hypertension (usual SBP $\geq$140 mm Hg)
diminishes with increasing numbers of consecutive measurements of “normal” SBP in the UK-TIA Trial and the Dutch TIA Trial. Measurements of BP in the ECST were insufficiently frequent after the first year to allow reliable analysis. As expected, consecutive measurements of SBP $\geq 140$ mm Hg with a mean of $\geq 120$ mm Hg were least likely to be associated with a subsequent usual SBP $\geq 140$ mm Hg in both trials, but 3 consecutive measurements were required to be $\geq 90\%$ certain that the subsequent usual SBP would not be $\geq 140$ mm Hg. In patients with 3 consecutive measurements of SBP $\geq 140$ mm Hg with a mean of 130 to 139 mm Hg, there was still a 25% to 30% chance of a subsequent usual SBP $\geq 140$ mm Hg.

Discussion

Variability in BP may be attributable to measurement error, short-term fluctuations, or longer-term changes. Previous estimates of CVs for measurement of BP have been mainly derived from ambulatory 24-hour recordings and relate to short-term variability, much of which will correspond with diurnal variation.\textsuperscript{15,24,25} There have been no other large studies of longer-term variability of daytime BP in patients with TIA, stroke, or other types of vascular disease. One small study of office BP variability in elderly hypertensive patients who had experienced a stroke suggested that long-term variability was high.\textsuperscript{26}

We have shown that in patients with TIA or stroke, single measurements of BP were poorly correlated with measurements taken a few months later. It is uncertain how much of the variability was attributable to short-term fluctuations or measurement error and how much was attributable to genuine medium-term variability. Previous studies suggest that short-term fluctuations during a single visit accounted for only $\approx 10\%$ of the variation between visits,\textsuperscript{17} and analysis of data from the Framingham study suggested that 6 repeated measurements gave the same reliability as a single measurement taken at 2 separate visits.\textsuperscript{27} It is likely, therefore, that most of the variability that we found represented genuine medium-term changes in BP and could not have been corrected for by multiple measurements at baseline or by 24-hour monitoring.

A number of factors may have contributed to the high medium-term variability of BP in our cohorts. First, our subjects were older than in previous general population studies and had higher absolute BP levels. Short-term BP variability, measured by 24-hour ambulatory monitoring, has been shown to increase with age and absolute BP,\textsuperscript{15,24,25} and the same could apply to medium-term variability. Second, most patients in our studies will have had some degree of chronic arterial disease, which is associated with decreased compliance of large elastic arteries, increased pulse pressure, and increased variability of BP.\textsuperscript{15,28,29} Third, there was some suggestion in our cohorts that BP variability was greater in patients with a previous stroke than in those with a previous TIA, and it is possible that this was a consequence of the stroke.\textsuperscript{30}
Our findings have implications for the interpretation of the results of trials of BP lowering after TIA or stroke. For example, the PROGRESS trial reported that BP lowering was highly beneficial in patients with a previous TIA or stroke, regardless of initial BP. It was therefore recommended that, unless contraindicated or not tolerated, all patients with a previous TIA or minor stroke begin taking a BP-lowering medication, irrespective of baseline BP. This concept is at odds with guidelines on the use of BP-lowering drugs in primary prevention, all of which have identified thresholds for treatment, usually 140/85 mm Hg. However, as in our trial populations, the baseline BP measurements in the PROGRESS trial are likely to have been poor measures of medium-term usual BP, and many patients will have been misclassified, thereby diminishing any genuine differences between groups in the expected benefit from treatment. Misclassification may have been even greater in the PROGRESS trial than in our populations because a higher proportion (60%) of PROGRESS patients were already taking BP-lowering drugs at baseline, and the majority had had a previous stroke rather than a TIA, both of which were associated with more marked variability in BP in each of our trial cohorts.

Our findings are not, however, at odds with the results of the PROGRESS trial. If the decision to start a BP-lowering drug is based on a single measurement of BP, then the analysis of the relation between baseline BP and relative benefit from treatment in PROGRESS is valid. However, uncertainty about benefit would remain in a patient in whom multiple measurements of SBP on separate visits were consistently $<120$ mm Hg, for example.

Our analyses have some potential shortcomings. First, patients contributing repeated measurements may not have been representative of the total cohorts at baseline, given that patients who died or had a stroke or coronary event during the first year of follow-up were excluded. However, the numbers of patients excluded for this reason were small (5% to 10%), and the mean BP at baseline in these cases did not differ significantly from those who were included. Second, there was no standardization between centers in the way in which BP was measured in any of the trials. However, because we were interested in intraindividual variability and all measurements in individual patients would have been made at the same center, usually by the same clinician, this should not undermine our findings. Moreover, the fact that measurements were made in much the same way as in real routine clinical practice is an advantage in terms of the generalizability of our findings. Third, we did not have data on changes to BP-lowering drugs during follow-up. However, the most likely change (ie, an increase in the proportion of patients taking such medication as follow-up progressed) would not account for our findings. Fourth, it could be argued that the variability in BP that we observed was attributable in some way to white coat hypertension. However, this seems unlikely, because all measurements in any individual were made in the same clinic environment on each occasion, usually by the same physician.

In conclusion, medium-term variability in BP in patients with a previous TIA or stroke is high, and single measurements of “normal” or “low” blood pressure will substantially underestimate the true prevalence of hypertension.

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Disclosures

None.

References


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