Monitoring Adherence to Medication by Measuring Change in Blood Pressure

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Abstract—After starting antihypertensives, blood pressure is monitored for several reasons, including assessment of adherence. We aimed to estimate the accuracy of blood pressure monitoring for detecting early nonadherence. We conducted a secondary analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), a large randomized trial of blood pressure lowering to reduce the risk of recurrent stroke. We compared change in blood pressure 3 months after randomization in people who had discontinued treatment (nonadherent) with those who stayed on treatment (adherent). We also used an indirect method, assessing whether change in blood pressure discriminated between active (adherent) and placebo (nonadherent) groups. Both methods gave similar results. For the 3433 subjects, the mean (SD) of the change in systolic blood pressure was -15.8 mm Hg (SD 18.7 mm Hg) in the adherent group and -4.2 mm Hg (SD 18.1 mm Hg) in the nonadherent group. After recalibration of the mean change in the nonadherent group to 0 mm Hg and in the adherent group to -11.6 mm Hg, the absence of a fall in systolic blood pressure at 3 months had a sensitivity of 50% and a specificity of 80% for detecting nonadherence (50% of nonadherent patients and 20% of adherent patients had a rise in blood pressure). Discriminatory power was modest over the range of cutoffs (area under the receiver–operator curve 0.67). Monitoring blood pressure is poor at detecting nonadherence to blood pressure–lowering treatment. Further research should look at other methods of assessing adherence. (*Hypertension.* 2010;56:612-616.)

Key Words: medication nonadherence ∎ blood pressure ∎ ROC curve ∎ angiotensin-converting enzyme inhibitors ∎ sensitivity and specificity

After starting a patient on blood pressure–lowering treatment, usual clinical practice is to regularly monitor blood pressure. Such blood pressure monitoring is undertaken to check initial response to treatment, monitor longer-term drift in the patient's blood pressure, and make an assessment of the patient's adherence to treatment. Recent reports question the value of current monitoring strategies for assessing the patient's initial[1,2] and longer-term response to treatment[3] because of the substantial usual background variability in an individual's blood pressure levels. The value of monitoring blood pressure for adherence has not been quantified.

Clinical guidelines suggest that nonadherence is a common cause of resistant hypertension (failure to achieve target blood pressure levels despite 3 treatments at maximal dose)[4,5] and suggest that if blood pressure remains above target, nonadherence to therapy is a likely explanation.[6] For example, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends to "consider nonadherence as a cause of: failure to reach goal blood pressure, resistant hypertension, sudden loss of control."[4] Broadly, nonadherence may be categorized into 2 types of imperfect drug-taking behavior:[7] either continuing to take therapy but at a dose or frequency that is less than that prescribed, or stopping taking therapy altogether (also referred to as discontinuation or nonpersistence). Nonadherence is thought to be an important reason why the full anticipated effect of therapies is not achieved in the community,[8] with adherence rates often substantially lower than those achieved in trial populations. Estimates of adherence in the community vary from 50% to 70%[8] compared with adherence rates of >80% in many trial populations.[9] Early discontinuation in particular appears to be a major problem, with a recent study reporting that 30% of patients prescribed long-term blood pressure–lowering medication discontinued within the first 100 days, 36% by 6 months, and 50% by 1 year.[10] The lower levels of adherence in community populations are attributed primarily to inadequate communication between physicians and their patients, although side effects and out-of-pocket cost may also contribute.[11]

Clinicians need a reliable method for detecting nonadherence so that interventions to enhance adherence may be directed appropriately[12] or alternate disease prevention strategies used. A range of different approaches has been used to assess adherence to therapy, including directly observed

therapy, measurement of blood drug levels, patient questionnaires, pill counts, prescription refill rates, electronic medication monitoring, and measurement of physiological markers such as blood pressure.[13]

The objective of this study was to evaluate the performance of blood pressure–monitoring as a means of detecting early nonadherence to blood pressure–lowering therapy. To achieve this, we analyzed changes in blood pressure from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS),[14] a randomized trial that defined the effects of blood pressure lowering on the risk of recurrent stroke.

Methods

Details of PROGRESS have been described previously.[14] In brief, this was a large-scale, multicenter, placebo-controlled, randomized trial that evaluated the effects of perindopril alone and perindopril together with indapamide (dual treatment) on the risk of cardiovascular events in 6105 patients with previous stroke or transient ischemic attack. The analyses in the current article are based on the dual treatment arm for which active treatment was a regimen of 4 mg of perindopril and 2.0 to 2.5 mg of indapamide daily, and control was double placebo. Data on blood pressure change from the baseline prerandomization assessment (made immediately before a 1-month run-in of active treatment) and the 3-month postrandomization visit were used. On each occasion, blood pressure was measured in exactly the same way, with 2 measurements taken 5 minutes apart with the patient in the seated position and each measurement being recorded to the nearest 2 mm Hg using a standard mercury sphygmomanometer. The mean of the 2 measurements was taken as the blood pressure level at the visit. Discontinuation of trial medication was ascertained by asking patients whether they were still taking therapy or not at the 3-month follow-up visit.

The analyses used change in blood pressure between baseline and follow-up recordings to determine the capacity of blood pressure measurement to detect nonadherent patients. We used 2 methods to define adherence. The first was the discontinuation comparison, which included only those patients randomly assigned to the active treatment group. In this analysis, those who reported continuing to take at least some of their study medication were considered adherent, and those who reported they had completely stopped taking any of their study medication were considered nonadherent. The second method was the placebo comparison, for which we considered patients in the active group to be equivalent to those patients prescribed blood pressure–lowering medication in clinical practice who are adherent and patients in the placebo group to be equivalent to those patients prescribed medication in clinical practice who are nonadherent. We used the observed distributions of blood pressure changes to calculate the likelihood that a given change in blood pressure would truly indicate nonadherence.

For each method of defining adherence, we first calculated descriptive statistics and plotted the distribution of changes in blood pressure for adherent patients and nonadherent patients. We then obtained a receiver–operator curve (ROC) to quantify the capacity of change in blood pressure to detect whether a patient was from the adherent or nonadherent group. In addition, we used the data from the placebo comparison method to construct a model of blood pressure change for adherent and nonadherent patients. In the first instance, the model assumed a 50:50 mixture of normal distributions for blood pressure change in active (adherent) and placebo (nonadherent) groups so as to simulate the situation in the trial in which approximately half were randomized to active treatment and half to placebo. We estimated the parameters of the 2 normal distributions using the observed mean and variance of blood pressure changes for the 2 groups. From this model, we estimated the post-test probability that an observed change in blood pressure was from the placebo group when the pretest probability was approximately 50%. We did this by computing likelihood ratios and using the Bayes theorem (for details, please see the online supplement, available at http://www.

hypertension.org). The modeled post-test probabilities of nonadherence were compared with the proportions actually observed to be in the placebo group for different levels of change in blood pressure. For the remainder of the modeled accuracy results, we recalibrated the trial data so that the mean blood pressure change in the placebo group was 0 mm Hg and the mean blood pressure change in the active group was the difference between the observed change in the active and placebo groups. We used the recalibrated model to estimate the post-test probability of nonadherence given a specific change in blood pressure, assuming different levels of population nonadherence (10%, 20%, 30%, 40%, and 50%).

The last set of analyses examined the impact of making multiple sets of measurements of blood pressure before and after starting therapy on the post-test probability of adherence. To do this, we assumed that the variance of change for n sets of measurements (with 2 measurements taken at each reading as in PROGRESS) before and after starting therapy was σ^2/n, where σ^2 is the variance of change for 1 set of before and after measurements.

For the primary analysis, we used change in systolic blood pressure. Analysis was also done using change in diastolic blood pressure.

Results

Discontinuation Comparison

There were 48 of the 1770 people commenced on active treatment who reported they had stopped all randomized treatment by 3 months after randomization. Of these, 30 had the required baseline and follow-up blood pressure readings. The mean (SD) change in blood pressure for the discontinuers (nonadherent) was a drop of 5.8 mm Hg (12.3 mm Hg) compared with a fall of 16.0 mm Hg (18.8 mm Hg) in the group still on therapy. The area under the ROC was 0.67 (95% CI, 0.59 to 0.75), indicating moderate discrimination. By 6 months, 89 people had discontinued the trial, and of these, 66 had blood pressure readings at baseline and 6 months. The area under the curve at 6 months after randomization was similarly moderate, at 0.62 (95% CI, 0.55 to 0.70).

At 3 months, the area under the curve for males was 0.70 (95% CI, 0.62 to 0.77) and 0.62 for females (95% CI, 0.44 to 0.80; ROCs not shown).

Placebo Comparison

There were 3433 subjects with systolic blood pressure measurements at 1 month before randomization and at 3 months after randomization. Of these, 1709 (49.6%) were in the active group and 1734 (50.4%) in the placebo group.

The mean (SD) of the change in systolic blood pressure was a fall of 15.8 mm Hg (18.7 mm Hg) in the active group and a fall of 4.2 mm Hg (18.1 mm Hg) in the placebo group; therefore, the difference in mean changes was 11.6 mm Hg. The observed distribution of these changes in systolic blood pressure is shown in Figure 1A, showing a substantial overlap in the distributions. The modeled distributions are shown in Figure 1B, both before (first, nonbold axis) and after (second, bold axis) recalibration of the mean change to 0 mm Hg in the placebo group and −11.6 mm Hg in the active group. If the absence of an observed fall in systolic blood pressure at 3 months was taken as an indicator of nonadherence, the sensitivity would be 50% and the specificity 73% (Figure 2; Table). That is, of those who were nonadherent, 50% would have recorded a rise in blood pressure (and 50% a fall) at 3 months; and of those who were adherent, some 27% would have recorded an apparent rise in blood pressure at 3 months despite taking their treatment. The sensi-
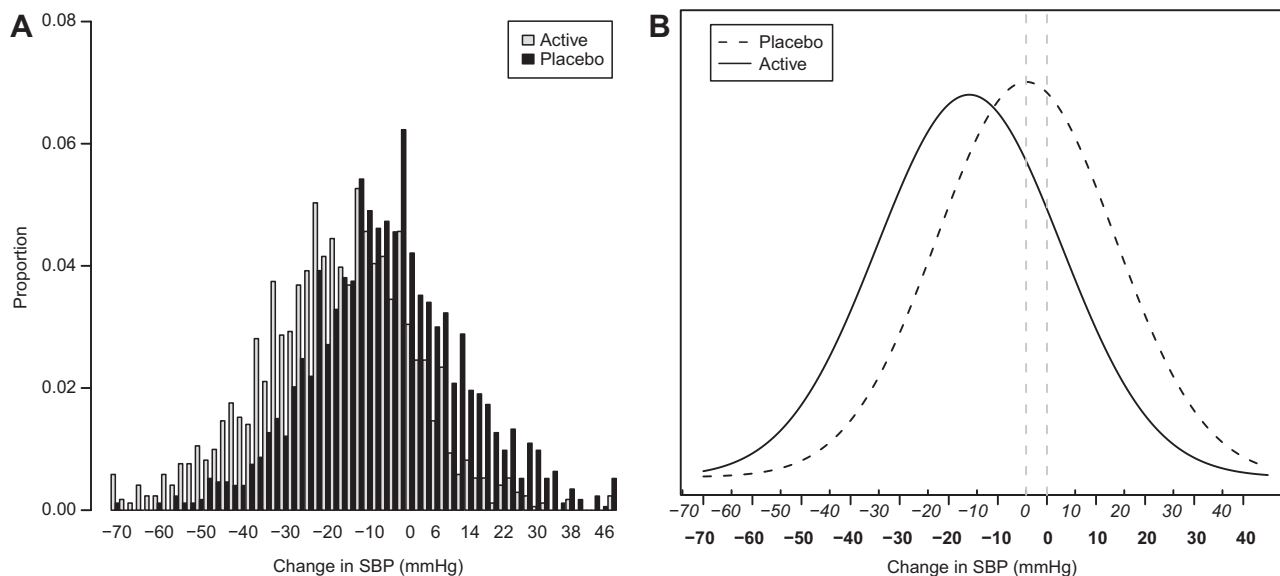
Figure 1. A, Observed change in systolic blood pressure (SBP) from baseline to 3-month follow-up, for active (adherent) and placebo (nonadherent) groups in the PROGRESS trial. B, Modeled change in systolic blood pressure from baseline to 3-month follow-up for active (adherent) and placebo (nonadherent) groups in the PROGRESS trial. The nonbold axis denotes the modeled data based on the observed distributions in A. The bold axis denotes the modeled data after recalibration of mean change to 0 mm Hg in the placebo group and −11.6 mm Hg in the active group.

tivity versus specificity tradeoffs for all possible cutoff values for change in blood pressure at 3 months are shown in Figure 2. The ROC confirms the modest discriminatory power of change in systolic blood pressure with the area under the curve being 0.67 (95% CI, 0.65 to 0.69). The area under the curve was the same for males 0.67 (95% CI, 0.65 to 0.69) and females 0.67 (95% CI, 0.63 to 0.70; ROCs not shown). The discriminatory power for change in diastolic blood pressure was even poorer, with an area under the curve of 0.63 (95% CI, 0.61 to 0.65; ROC curve not shown).

Effects of Different Rates of Nonadherence
The analyses reported in Figure 2 are based on a ratio of adherent to nonadherent patients of ≈1:1 because this was the
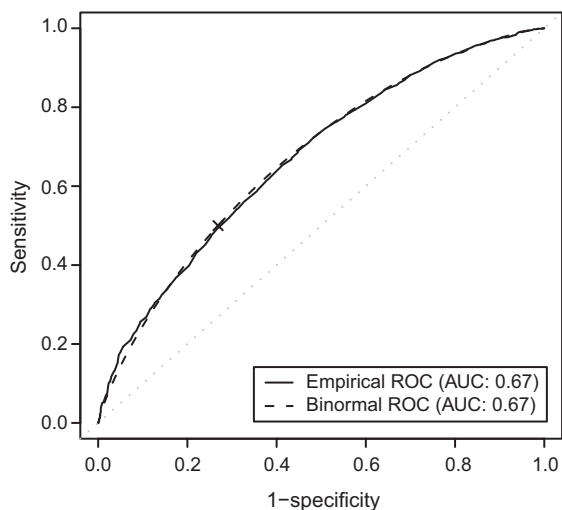

Figure 2. Empirical and binormal ROC for changes in systolic blood pressure from baseline to 3-month follow-up. The cross indicates the sensitivity and 1-specificity at a cutoff of a change in systolic blood pressure of 0 mm Hg. AUC indicates area under the curve.

randomization ratio in the PROGRESS trial. However, in practice, this ratio is unlikely, with adherent individuals substantially outnumbering nonadherent individuals in most patient populations. In Figure 3, we show the probability of detecting nonadherence for given changes in systolic blood pressure at various background levels of nonadherence in the patient population. This shows that even in populations with relatively high background rates of nonadherence (eg, 30% of the population is nonadherent), patients who have modest rises in blood pressure are still more likely to be adherent that nonadherent. In populations with low background nonadherence rate rises, the problem is even more marked.

Effects of Making Sets of Multiple Blood Pressure Measurements
Increasing the number of measurements from which the mean blood pressure is determined before and after the commencement of treatment greatly enhances the capacity of change in blood pressure to differentiate between adherent and nonadherent individuals. For estimates of change in systolic blood pressure that use the average of 2 sets of readings before and 2 sets of readings after, the area under the ROC is 0.73. If, instead, there were 10 sets of measurements made both before and after, the area under the ROC rises to 0.92. In practical terms, this means that if the failure of systolic blood pressure to fall was taken as an indicator of nonadherence on the basis of 2 sets of before–after measurements (ie, 2 sets of measurements at separate clinic visits), we would have a sensitivity of 50% and a specificity of 81%. If 10 measurements were made before and after treatment, the corresponding figure would be 50% and 97% (Table). In other words, if duplicate sets of before–after blood pressure measurements were taken, 5 out of every 10 nonadherent individuals would correctly be identified as being nonadherent. In addition, ≈2 out of every 10 adherent individuals would be incorrectly identified as being nonadherent. If 10 sets of

Table. Sensitivity and Specificity of Different Thresholds of Change in Blood Pressure From Baseline to 3-Month Follow-Up for the Detection of Nonadherence With Varying Numbers of Blood Pressure Readings Before and After Treatment Commencement

Drop in Systolic Blood Pressure (mm Hg)			<20		<15		<10		<5		0 or Increase	
Sets of Readings Before Treatment	Sets of Readings After Treatment	Area Under ROC	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
1	1	0.67	87	33	80	43	71	53	61	64	50	73
2	2	0.73	94	26	88	40	78	55	65	69	50	81
5	1	0.72	92	28	86	41	76	54	64	67	50	79
5	2	0.77	97	22	92	38	82	56	68	72	50	85
5	5	0.85	99	16	97	34	89	57	72	78	50	92
10	1	0.72	93	27	87	40	77	54	65	68	50	80
10	2	0.79	98	21	93	37	84	56	69	74	50	87
10	5	0.87	100	12	98	32	92	58	76	82	50	94
10	10	0.92	100	8	100	28	96	60	81	87	50	97

Sens indicates sensitivity; Spec, specificity.

before–after measurements were used, 5 out of every 10 nonadherent individuals would correctly be identified as being nonadherent and 3 out of every 100 adherent individuals would incorrectly be identified as being nonadherent.

Interpretation

Our empirical and modeled results show that monitoring the change in blood pressure before and after commencing blood pressure–lowering treatment is not a good method for detecting early nonadherence to therapy. The combined effect of the substantial usual background variability in blood pressure with the relatively low prevalence of nonadherence found in most clinical populations means that the results of standard clinical monitoring may be importantly misleading in many cases. This is because the magnitude of the noise resulting from the within-person variation in blood pressure is large compared with the fall in blood pressure typically achieved with antihypertensive therapy. Reliability can clearly be improved by taking multiple measurements before and after therapy, and this could be achieved through the use of home blood pressure monitor-

Figure 3. Probability of a patient being truly nonadherent for a given change in systolic blood pressure (SBP) from baseline to 3 months for background population rates of nonadherence, varying between 10% and 50%.

ing.[15] However, our modeling (Table) suggests this would need to be ≥10 sets of before and after measurements, and even then, the sensitivity remains poor, meaning that many cases of nonadherence would still be missed.

There are some limitations in our estimations of the detectability of nonadherence. First, we used the trial active group to estimate the distribution of blood pressure change for an adherent population, although this is likely to include some partially and fully nonadherent individuals. However, because the reported adherence in PROGRESS at 3 months was very high (only 2.7% of participants in the dual therapy and active arm had discontinued by 3 months), we believe this is unlikely to be a major limitation. Second, we made estimates for full adherence (active group) to no adherence (the placebo group), although partial adherence is arguably the more common clinical problem. Patients who stop taking their pills altogether may volunteer this information to their doctor or simply stop showing up to clinic, but those who continue to take some of their pills may not be as forthcoming about their nonadherence. The capacity of blood pressure monitoring to detect partial adherence is likely to be even poorer than we have shown it to be for detecting complete nonadherence because the change in blood pressure would be less different from the fully adherent and even harder to pick out against the background noise. It is also of note that our analyses were made for adherence to a combined drug regimen (ACE inhibitor plus diuretic), in which the difference in blood pressure between adherent and nonadherent individuals was relatively large. For single drug regimens, in which the difference in blood pressure between adherent and nonadherent individuals would be smaller, the capacity of blood pressure monitoring to detect nonadherence would be more limited. In general, blood pressure monitoring would perform better as a means of detecting nonadherence where the effects of the regimen were large and worse where they were small. However, on the basis of these analyses, there appear to be few settings in which it is likely that blood pressure monitoring would be both a sensitive and specific means of detecting nonadherence to therapy.

Our study evaluated blood pressure monitoring as a means of detecting nonadherence early after the commencement of treatment. The identification of nonadherence after longer periods of
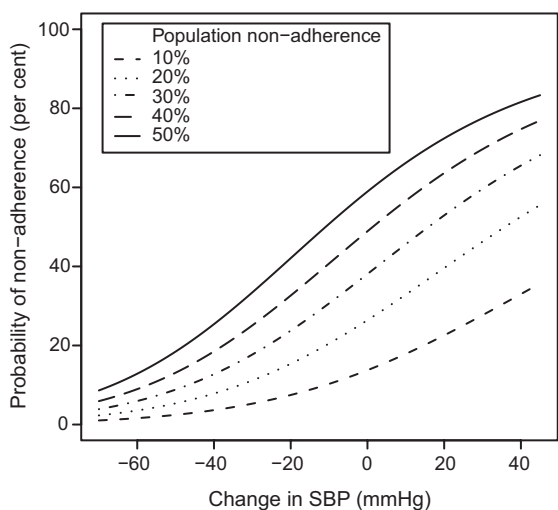
treatment[10,16,17] is also an important clinical issue but would include an additional complication. Blood pressure tends to drift gradually upward over time in even fully adherent patients, and the rate of that drift varies substantially between individuals. For blood pressure monitoring to reliably detect nonadherence in the longer term, it would need to distinguish change in blood pressure attributable to nonadherence not only from short-term background variability but also from this additional longer-term variability in an individual's blood pressure level. Additional work is needed to establish the value of blood pressure monitoring as a means of detecting nonadherence in the longer term, but it seems likely that the capacity to correctly discriminate between adherent and nonadherent patients will be worse than in the early treatment period.

Our results align with the findings of several other studies that examined the relationship between change in blood pressure and adherence and support the use of different approaches to monitoring and achieving adherence. A recent systematic review of studies that used electronic monitoring of the opening of medicine containers to measure adherence reported that when patients were categorized according to their achieved blood pressure, there was no association with measured adherence.[9] In contrast, patient interview methods have been found to correlate with adherence to blood pressure–lowering therapy,[18] and making patients an active part of treatment decisions has also been found to increase adherence.[19] Rather than a formal patient interview, a practical approach is for clinicians to simply ask the patient if he or she is having problems adhering to treatment, but the question needs to be framed in a nonjudgmental way that puts the patient at ease. One suggestion is: "I know it must be difficult to take all your medications regularly. How often do you miss taking them?"[13] Other questions that may help identify poor adherence include asking patients whether they are having side effects from the medication, why they believe they are taking the medication, and what they believe are the benefits of treatment.[13]

Perspectives

In conclusion, monitoring blood pressure appears to be a poor method of detecting nonadherence to blood pressure–lowering treatment, and it seems unlikely that this could easily be resolved by using different methods to assess blood pressure. Clinical practice guidelines need to be updated to reflect the limitations of blood pressure measurement as a means of detecting nonadherence and make other recommendations about how this can be achieved. Further research to identify effective ways of detecting nonadherence should probably focus on methods other than blood pressure measurement, or else to objectively test the feasibility and cost-effectiveness of using multiple home measurements.

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