Monitoring Initial Response to Angiotensin-Converting Enzyme Inhibitor–Based Regimens

An Individual Patient Data Meta-Analysis From Randomized, Placebo-Controlled Trials

Katy J.L. Bell, Andrew Hayen, Petra Macaskill, Jonathan C. Craig, Bruce C. Neal, Kim M. Fox, Willem J. Remme, Folkert W. Asselbergs, Wiek H. van Gilst, Stephen MacMahon, Giuseppe Remuzzi, Piero Ruggenenti, Koon K. Teo, Les Irwig

Abstract—Most clinicians monitor blood pressure to estimate a patient's response to blood pressure–lowering therapy. However, the apparent change may not actually reflect the effect of the treatment, because a person's blood pressure varies considerably even without the administration of drug therapy. We estimated random background within-person variation, apparent between-person variation, and true between-person variation in blood pressure response to angiotensin-converting enzyme inhibitors after 3 months. We used meta-analytic mixed models to analyze individual patient data from 28 281 participants in 7 randomized, controlled trials from the Blood Pressure Lowering Trialists Collaboration. The apparent between-person variation in response was large, with SDs for change in systolic blood pressure/diastolic blood pressure of 15.2/8.5 mm Hg. Within-person variation was also large, with SDs for change in systolic blood pressure/diastolic blood pressure of 14.9/8.45 mm Hg. The true between-person variation in response was small, with SDs for change in systolic blood pressure/diastolic blood pressure of 2.6/1.0 mm Hg. The proportion of the apparent between-person variation in response that was attributed to true between-person variation was only 3% for systolic blood pressure and 1% for diastolic blood pressure. In conclusion, most of the apparent variation in response is not because of true variation but is a consequence of background within-person fluctuation in day-to-day blood pressure levels. Instead of monitoring an individual's blood pressure response, a better approach may be to simply assume the mean treatment effect. **(*Hypertension*. 2010;56:533-539.)**

Key Words: blood pressure ■ angiotensin-converting enzyme inhibitors ■ treatment outcome ■ models ■ statistical ■ reproducibility of results ■ cardiovascular disease ■ stroke

Blood pressure is a well-established important modifiable risk factor for vascular disease. Randomized, controlled trials of blood pressure–lowering therapies have demonstrated substantial clinical benefits of lowering blood pressure in populations at increased risk of vascular disease,[1] and angiotensin-converting enzyme (ACE) inhibitors are one of the widely used blood pressure–lowering drugs.[2]

Although the benefits of taking ACE inhibitors are well established, the value of monitoring individuals' blood pressure responses after the commencement of therapy is not understood. The purpose of "initial response" monitoring is to estimate an individual's initial response to treatment by measuring blood pressure soon after treatment is started. However, the substantial background variability of an individual's blood pressure may conceal the true effects of the drug treatment.[3] For example patient blood pressure levels commonly vary by ≥20 mm Hg between clinic visits,[4] whereas the effects of drug treatments observed in clinical trials are typically much smaller than this. The large background variation may result in the effects of the drug being overestimated or underestimated by the clinician and inappropriate changes being made to therapy. Current clinical

Received February 24, 2010; first decision March 20, 2010; revision accepted June 14, 2010.

From the Screening and Test Evaluation Program (K.J.L.B., A.H., P.M., J.C.C., L.I.), School of Public Health, University of Sydney, Sydney, New South Wales, Australia; Department of Nephrology (J.C.C.), Children's Hospital at Westmead, Westmead, New South Wales, Australia; George Institute for International Research (B.C.N., S.M.), Royal Prince Alfred Hospital, University of Sydney, Sydney, New South Wales, Australia; Cardiology Department (K.M.F.), Royal Brompton Hospital, London, United Kingdom; Sticares Cardiovascular Research Foundation (W.J.R.), Rhoon, The Netherlands; Department of Cardiology, University Medical Center Groningen (F.W.A.), and Department of Clinical Pharmacology (W.H.v.G.), University of Groningen, Groningen, The Netherlands; Mario Negri Institute for Pharmacological Research and Unit of Nephrology (G.R., P.R.), Azienda Ospedaliera Ospedali Riuniti di Bergamo, Bergamo, Italy; Department of Medicine (Cardiology) (K.K.T.), McMaster University, Hamilton, Ontario, Canada.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

Correspondence to Katy J.L. Bell, Screening and Test Evaluation Program, School of Public Health, Edward Ford Building (A27), University of Sydney, NSW 2006, Australia. E-mail katyb@health.usyd.edu.au

Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.110.152421**

practice guidelines recommend initial response monitoring of blood pressure after starting blood pressure–lowering therapy but do not account for background variability.[5,6]

Our study objective was to assess the value of initial response monitoring of blood pressure after starting an ACE inhibitor–based regimen. We achieved this by comparing the variation in blood pressure for patients on treatment with that for patients on placebo to unpack the overall apparent between-person variation in response to ACE inhibitors into its component parts. Overall apparent between variation in response was disaggregated into variation because of true between-person variation in response and variation because of random background within-person variation. Initial response monitoring may be clinically useful when true between-person variation in response is large and random background within-person variation in blood pressure is small.

Methods

Study Design and Participants

The trials included in this study were those studies of ACE inhibitor–based regimens included in the Blood Pressure Lowering Treatment Trialists Collaboration,[7] an international program that collects data prospectively from trials of blood pressure–lowering treatments. Trials were eligible for inclusion if they randomized patients to an ACE inhibitor–based regimen or placebo, had ≥3 measurements of blood pressure made in the first year after randomization, and data were available by June 2007. For trials evaluating >1 blood pressure–lowering treatment, only data from the ACE inhibitor–based and placebo arms of the trial were included. Trials also met the other inclusion criteria for the collaboration, including a minimum of 1000 patient-years of planned follow-up in each randomized group and no presentation or publication of main results before the collaboration finalized the protocol in July 1995.[7]

Outcome Measures

We fitted separate longitudinal models for systolic blood pressure and diastolic blood pressure. For each type of blood pressure outcome we used the average of 2 blood pressure measurements made at 3, 6, and 12 months after randomization (the first clinic visit for Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation was at 4 months after randomization). Pretreatment blood pressure (measured before starting the trial) was included as a predictor of later (on-treatment) blood pressure measurement. The primary findings are based on treatment effects on blood pressure measured at 3 months.

Statistical Analysis

We first fitted a series of statistical models for each trial that took into account the correlation that exists between repeated measurements in a longitudinal data set. This type of model is commonly referred to as a "mixed model." We used the mixed models to estimate the mean treatment effect, the true between-person variation in treatment effects, and the background random within-person variation in blood pressure that is unrelated to treatment. Within-person variation in change in blood pressure before and after starting treatment was estimated by taking the square root of the within-person variances on placebo and ACE inhibitor treatment. A detailed explanation on how mixed models may be used to estimate variation in treatment effects is provided in a previous report.[3]

We then extended the mixed models method to allow meta-analysis of pooled data from all of the trials. The modeling strategy was similar to that for the within-trial analysis, the main difference being that covariates were included in the meta-analytic models to represent the separate trials.

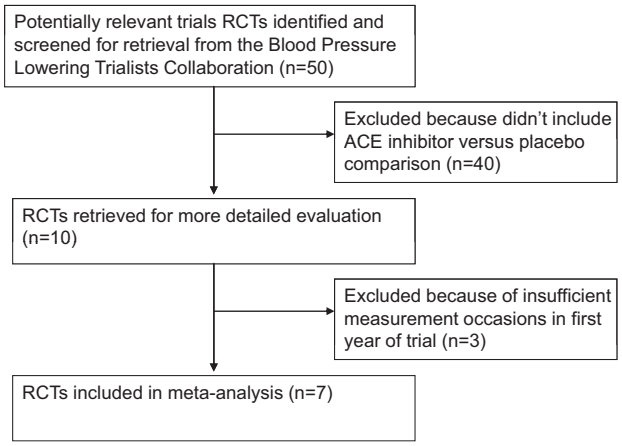

Figure 1. Flow diagram describing selection of trials for meta-analysis.

We estimated between-person variation in treatment effects in a number of ways. For each trial, the true between-person variation (SD) of treatment effects was calculated by taking the square root of each trial-specific model estimate of between person variance in treatment effects. These estimates do not include background within-person variation. The corresponding apparent between-person variation (SD) of treatment effects were estimated from the observed changes for participants in the ACE inhibitor arms of the trials and include background within-person variation.

For the pooled estimates, the true between-person variation (SD) of treatment effects was calculated by taking the square root of the meta-analytic model estimate of between-person variance in treatment effects (T). The apparent between-person variation (SD) of treatment effects was calculated by summing the meta-analytic model estimates of between-person variance in treatment effects (T) and within-person variance of change in blood pressure (W), and then taking the square root (apparent variation$=\sqrt{T+W}$). The proportion of apparent variation in treatment effects that was true was then estimated (proportion$=T/(T+W)$). (Within-person variation of change in blood pressure includes within-person variation of measurements before and after treatment is started.)

The 95% distribution of treatment effects for each estimate was calculated as mean treatment effect$\pm 1.96\times$SD of treatment effects.

Further explanations of the model fitting for the individual trials and the meta-analysis are provided in the online Data Supplement (please see http://hyper.ahajournals.org). Analysis was done using MLwiN, with models fitted using iterative generalized least squares (Centre for Multilevel Modeling, University of Bristol).

Results

Characteristics of Trials Included

The selection of trials that were included in these analyses is summarized by the flow diagram in Figure 1. Of 50 potentially relevant trials in the Blood Pressure Lowering Treatment Trialists Collaboration,[8] 10 randomized, controlled trials included an ACE inhibitor versus placebo comparison. Three of these trials were excluded because of insufficient measurement occasions in the first year,[9–11] leaving 7 trials that were finally included.[12–18] The included trials ranged in size from 460 participants to 12 218 participants, with an overall total of 28 281 participants. The salient features of the trials varied and are described in Table 1. Although all of the trial populations were at higher risk of macrovascular disease than the general population, there were substantial differences in the disease rates observed. Over 3.6 years (Bergamo Nephrologic Diabetes Complications Trial) to 4.7 years

Table 1. Characteristics of Included Trials (Ordered by Size)

Trial	Date Published	No. Included in Analysis	Features of Trial Population	ACE Inhibitor	Mean Baseline Systolic Blood Pressure (SD)	Background Macrovascular Event Rate, % (Years of Follow-Up)*	Frequency of Blood Pressure Measurement in First Year After Randomization	Details of Blood Pressure Measurement
EUROPA[12]	2003	12 218	Ischemic heart disease	Perindopril 8 mg	137.1 (15.5)	11.5 (4.2)	3, 6, 12 mo	Average of 2 measurements taken with standard sphygmomanometer after ≥5 min of rest
ADVANCE[13]	2007	11 140	Type 2 diabetes mellitus, ischemic heart disease or other risk factor	Perindopril 4 mg†	145.0 (21.5)	9.0 (4.3)	4, 6, 12 mo	Average of 2 measurements taken with standard automatic sphygmomanometer after ≥5 min of rest in seated position
PROGRESS (Single Treatment Arm)[14]	2001	2455	High risk of stroke	Perindopril 4 mg	143.7 (18.7)	18.5 (3.9)	1, 3, 6, 9, 12 mo	Average of 2 measurements taken to nearest 2 mm Hg with standard mercury sphygmomanometer
PREVEND IT[15]	2004	864	Microalbuminuria	Fosinopril 20 mg	130 (17.6)	6.5 (4 y)	2 wk, 3, 6, 9, 12 mo	Average of last 2 of 10 consecutive measurements taken with an automatic sphygmomanometer (Dinamap XL)
PART2[16]	2000	617	Ischemic heart disease or peripheral vascular disease	Ramipril 10 mg‡	133.0 (16.7)	25.0 (4.7 y)	1, 3, 6, 9, 12 mo	Average of 2 measurements taken to nearest 2 mm Hg with standard mercury sphygmomanometer
BENEDICT[17]	2004	527	High blood pressure, type 2 diabetes mellitus, microalbuminuria	Trandolapril 2 mg	151.4 (15.1)	5.0 (3.6 y)	1 wk, 3, 6, 9, 12 mo	Average of 3 measurements taken in the morning with a manual sphygmomanometer, before administration of a study drug
SCAT[18]	2000	460	Ischemic heart disease or high risk of ischemic heart disease	Enalapril 2.5 mg	129.7 (19.4)	13.0 (4 y)	3, 6, 9, 12 mo	No set protocol as to how many measurements taken; standard mercury sphygmomanometers used

*Data are as reported in placebo arm of the trial. Macrovascular events include nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death.

†Active treatment included indapamide 1.25 mg.

‡Seventeen percent of those on active treatment had ramipril 5 mg rather then ramipril 10 mg.

EUROPA, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; PROGRESS, Perindopril Protection against Recurrent Stroke Study; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; PART2, Prevention of Atherosclerosis with Ramipril; BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; SCAT, Simvastatin/Enalapril Coronary Atherosclerosis Trial.

(Prevention of Atherosclerosis with Ramipril) of follow-up, the macrovascular event rates ranged from 6.5% (in Prevention of Renal and Vascular Endstage Disease Intervention Trial) to 25.0% (in PART2). In addition, a range of different ACE inhibitors was evaluated: perindopril (3 trials), ramipril (1 trial), fosinopril (1 trial), enalapril (1 trial), and trandolapril (1 trial).

Apparent and True Variation of Treatment Effects Between Individuals for Each Trial

The apparent between-person variation in the response of blood pressure to ACE inhibitor therapy for the participants of each separate trial was large and is shown in Table 2. By contrast, the estimated true between-person variation in the response of blood pressure to ACE inhibitor therapy was much smaller. For 2 of the smaller trials, there was statistically significant evidence of variation in true treatment effects on systolic blood pressure between trial participants (Prevention of Renal and Vascular Endstage Disease Intervention Trial and Prevention of Atherosclerosis with Ramipril), but there was no such evidence for the 3 larger trials (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation, and Perindopril Protection against Recurrent Stroke Study). For the 2 smallest trials the models gave estimates of variation in true treatment effects that were <0 (Bergamo Nephrologic Diabetes Complications Trial and Simvastatin/Enalapril Coronary Atherosclerosis Trial). Where the number of participants in a trial is small or the between-person variation in response is very close to 0, the capacity of the statistical models to provide an estimate of

Table 2. Mixed Models of Blood Pressure for ACE Inhibitor Trials (3 Months After Treatment Started)

Type of Blood Pressure	Trial	Mean Effect of ACE Inhibitor (Lowering of Blood Pressure), mm Hg	Apparent Between-Person Variation in Effects of Treatment (SD), mm Hg*	True Between-Person Variation in Treatment Effects (SD), mm Hg†	Apparent Distribution of Treatment Effects (5th, 95th Percentiles), mm Hg*	True Distribution of Treatment Effects (5th, 95th Percentiles), mm Hg†
Systolic	EUROPA	−5.1	15.8	2.4	−36.1, 25.9	−10.2, −0.2
	ADVANCE	−7.5	20.2	1.7	−47.1, 32.1	−10.4, −4.6
	PROGRESS	−6.3	17.3	3.0	−40.2, 27.6	−11.8, −1.4
	PREVEND IT	−6.9	13.8	5.8§	−33.9, 20.1	−18.2, 4.3
	PART2	−7.1	16.3	6.4§	−39.0, 24.8	−19.6, 5.3
	BENEDICT	−3.3	13.7	Not estimable‖	−30.2, 23.6	Not estimable‖
	SCAT	−9.7	17.5	Not estimable‖	−44.0, 24.6	Not estimable‖
	All trials (meta-analysis)	Trial-specific mean effect	15.2‡	2.6	Trial-specific mean effect±29.7‡	Trial-specific mean effect±5.0
Diastolic	EUROPA	−2.5	9.8	1.3	−21.7, 16.7	−5.0, 0.0
	ADVANCE	−2.9	10.4	0.8	−23.3, 17.5	−4.5, −1.3
	PROGRESS	−3.1	10.6	Not estimable‖	−23.0, 17.7	Not estimable‖
	PREVEND IT	−3.9	7.1	2.6§	−17.8, 10.0	−9.0, 1.2
	PART2	−3.7	9.7	2.7	−22.7, 15.3	−9.1, 1.6
	BENEDICT	−2.1	7.3	Not estimable‖	−16.4, 12.2	Not estimable‖
	SCAT	−5.7	10.1	Not estimable‖	−25.5, 14.1	Not estimable‖
	All trials (meta-analysis)	Trial-specific mean effect	8.5‡	1.0	Trial-specific mean effect±15.2‡	Trial-specific mean effect±1.9

*Estimates of apparent between-person variation in treatment effects are from variation in changes in blood pressure observed in ACE inhibitor arms of trials.

†Estimates of true between-person variation in treatment effects are from mixed models, where between-person variation and background within-person variation are disaggregated.

‡Apparent pooled variation in treatment effects is estimated from sum of the variance of treatment effects and variance of within-person change in blood pressure.

§Between-person variation in treatment effects is significant ($P<0.05$).

‖Models failed to produce estimates of between-person variance in treatment effects that were >0.

EUROPA, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; PROGRESS, Perindopril Protection against Recurrent Stroke Study; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; PART2, Prevention of Atherosclerosis with Ramipril; BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; SCAT, Simvastatin/Enalapril Coronary Atherosclerosis Trial.

the variation in treatment effects between individuals is limited. The results for treatment effects on diastolic blood pressure showed a similar pattern to the results for systolic blood pressure.

Meta-Analysis of Treatment Effects

For systolic blood pressure, there was very strong evidence that the mean treatment effect differed among the 7 trials ($P<0.001$; Table 2). There was also evidence from the pooled analysis that the blood pressure–lowering effect was more pronounced in older patients compared with younger patients (treatment lowered systolic blood pressure by an extra 0.5 mm Hg for every 10 years of age; $P=0.001$) and declined over time (by ≈1 mm Hg over the first year of treatment; $P=0.01$). There was no evidence that the blood pressure–lowering effect differed according to pretreatment blood pressure ($P=0.13$), sex ($P=0.16$), or body mass index ($P=0.65$). There was no evidence that the between-person variation in treatment effects differed among the trials ($P=0.19$) and overall estimates of between-person variation in treatment effects were therefore calculated pooling data from all of the trials. These analyses provided weak evidence of between-person variation in the effects of ACE inhibitor therapy on systolic blood pressure ($P=0.03$). The SD of true treatment effects on systolic blood pressure was estimated as 2.6 mm Hg, and 95% of individuals had a true change in blood pressure that was within 5.1 mm Hg of the mean change achieved in their trial. The SD of background within-person variation in systolic blood pressure was estimated as 10.4 on placebo, 10.8 mm Hg on ACE inhibitor treatment, and 14.9 mm Hg for change before and after treatment. The SD of apparent treatment effects on systolic blood pressure was estimated as 15.2 mm Hg, and 95% of individuals had an apparent change in blood pressure that was within 29.7 mm Hg of the mean change achieved in their trial. The proportion of the observed variance of change in systolic blood pressure after starting treatment that was actually because of true between-person variance in the response to ACE inhibitors was estimated as 3% (see Figure 2A), with the remaining 97% attributable to usual day-to-day within-person fluctuations in blood pressure.

The results of the diastolic blood pressure analysis showed a similar pattern (Table 2). There was very strong evidence that the mean treatment effect differed among the 7 trials ($P<0.001$), but there was no evidence that the mean treatment effects varied with age ($P=0.44$), time ($P=0.44$),

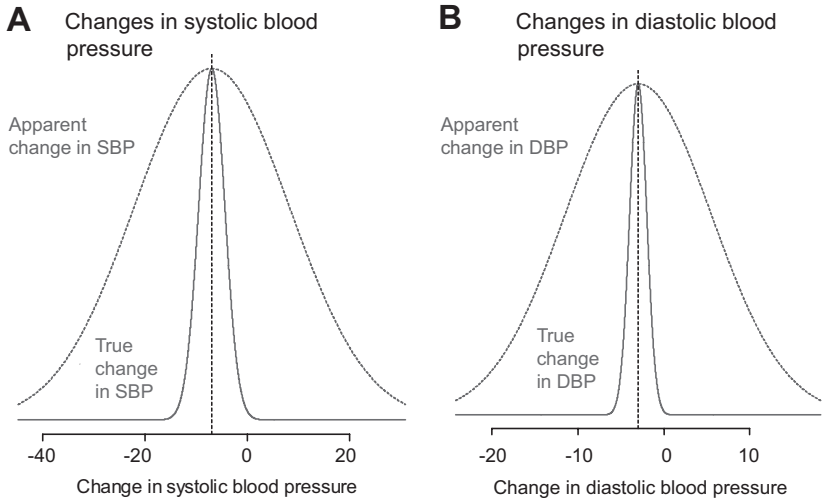

Figure 2. Distribution of apparent and true changes in blood pressure after starting an ACE inhibitor.

The pairs of normal distribution curves have been constructed to have the same height and the area under each curve is proportional to the standard deviation of change in blood pressure. The proportion of the apparent variation in blood pressure change that is due to true between person variation in treatment effects is small. Only 3% of the apparent variance in systolic blood pressure change and 1% of the apparent variance in diastolic blood pressure are due to true between person variance in treatment effects. (Proportion is calculated from: between person variance in treatment effects / (between person variance in treatment effects + within person variation in blood pressure change)).

pretreatment blood pressure ($P=0.58$), sex ($P=0.13$), or body mass index ($P=0.53$). Because there was no strong evidence that the between-person variation in treatment effects differed among the trials ($P=0.06$), estimates of between-person variation were calculated using the pooled data from all of the trials. These analyses provided little evidence of between-person variation in the effects of ACE inhibitor therapy on diastolic blood pressure ($P=0.10$). The SD of true treatment effects on diastolic blood pressure was estimated as 1.0 mm Hg, and 95% of individuals had a true change in blood pressure that was within 1.9 mm Hg of the mean change achieved in their trial. The SD of background within-person variation in diastolic blood pressure was estimated as 5.9 mm Hg on placebo, 6.0 mm Hg on ACE inhibitor treatment, and 8.45 mm Hg for change before and after treatment. The SD of apparent treatment effects on diastolic blood pressure was estimated as 8.5 mm Hg, and 95% of individuals had a true change in blood pressure that was within 15.2 mm Hg of the mean change achieved in their trial. The proportion of the observed variance of change in diastolic blood pressure after starting treatment that is attributed to true between-person variance in the response to ACE inhibitors was estimated as 1% (see Figure 2B).

Discussion

Using data from >28 000 patients in 7 trials of ACE inhibitors, which evaluated the effects of different agents within the same drug class and in different populations, we found that, after allowing for different mean blood pressure responses among the trials, there was only weak evidence of true between-person variation in blood pressure response. Furthermore, the magnitude of the variation was small: 95% of patients had a true change in systolic blood pressure that was within 5.1 mm Hg of the mean reduction for their trial with a corresponding figure of 1.9 mm Hg for diastolic blood pressure. This level of variability was much less than might be inferred from the apparent variation in response: 95% had an apparent change in systolic blood pressure that was within 29.7 mm Hg of the mean reduction for their trial with a corresponding figure of 15.2 mm Hg for diastolic blood pressure. Indeed, of the apparent between-person variation in treatment effects, we estimated that true between-person variation in response to ACE inhibitors was only 3% for systolic blood pressure and 1% for diastolic blood pressure. The majority of the apparent between-person variation in treatment response was actually because of background within-person variation, with SDs for change in systolic and diastolic blood pressures of 14.90 and 8.45 mm Hg. These figures are based on within-person SDs for a single measurement occasion (where 2 BP measurements are averaged) of systolic and diastolic blood pressures of 10.8 mm Hg and 6.0 mm Hg, respectively, similar to estimates we[19,20] and others[4,21] have reported previously.

The differences between the distributions of apparent change and true change that are illustrated in Figure 2 have substantial practical implications. There is a very high probability that any given individual will truly have some sort of decrease in systolic blood pressure after starting an ACE inhibitor with a population mean blood pressure–lowering effect of 6.5 mm Hg (95% distribution of true treatment effects: blood pressure lowered by 1.4 to 11.6 mm Hg). Given this information we have before monitoring the individual's response, we will usually need a very large number of measurements before and after treatment to further refine the probability of response by monitoring their blood pressure. For example, by monitoring an individual's blood pressure after starting treatment, clinicians may aim to determine whether treatment is working as expected (is there a substantial effect?), and whether treatment is having any effect at all (is there an effect?). Using the same example of treatment

with a mean blood pressure–lowering effect of 6.5 mm Hg, we estimate that it would be necessary to average >90 measurement occasions both before and after starting treatment to be 95% certain that an apparent decrease of >4 mm Hg in systolic blood pressure indicates a true decrease of >4 mm Hg (ie, to be certain that treatment is having a substantial effect). More than 5000 measurement occasions are needed before and after starting treatment to be 95% certain that an apparent decrease of <4 mm Hg indicates a true decrease of <4 mm Hg (ie, to be certain that treatment is not having a substantial effect). Only one measurement occasion is needed before and after starting treatment to be 95% certain that any apparent decrease indicates a true decrease in blood pressure (ie, to be certain that treatment is having any effect at all). But in this case monitoring is not adding anything to the information that we already had from the trials: nearly everyone will have some sort of decrease in blood pressure as a result of treatment. In contrast, we need >10 000 measurement occasions before and after starting treatment to be 95% certain that an apparent increase indicates a true increase in blood pressure (ie, to be certain that treatment is having no effect at all; see the online Data Supplement for calculations). These estimates indicate that to meet most of the common monitoring objectives, it is not feasible to make enough blood pressure measurements (even with the use of home blood pressure monitoring or 24-hour blood pressure monitoring) to separate the treatment effect from the within-person day-to-day variation in blood pressure. Rather than trying to estimate treatment effect for the individual using initial response monitoring, a more practical approach is to simply apply the treatment effects observed in trials.

Instead of using a "treat-to-target" approach of lowering blood pressure to a specific target, recent evidence suggests that a "fire and forget" approach may be preferred. Using this strategy, individuals at increased absolute risk of a cardiovascular event are given drugs to lower blood pressure and cholesterol regardless of single risk factor levels.[22,23] However, many clinicians may be uncomfortable with abandoning blood pressure targets altogether. In this case, rather than monitoring initial response to treatment, a better approach would be simply to estimate the treatment effect in an individual from the mean treatment effect observed in trial data obtained in a clinically and demographically similar population.

Estimating how baseline pretreatment blood pressure compares with a recommended target may be approximately calculated using the mean of ≥6 measurements.[24,25] The uncertainty surrounding the estimation of baseline using the average of 6 measurements is approximately the true level ±3 mm Hg.[25] (It should be noted that although this level of uncertainty is likely to be acceptable for deciding whether to start an individual on treatment, it is unlikely to be acceptable for deciding response to treatment. If only 6 measurements were used for both baseline and posttreatment levels, then the estimation of change would be approximately true change ±6 mm Hg. This level of uncertainty is too high to determine what the effect of treatment is for the individual, and a more sensible approach is to apply the mean treatment effect, as we have suggested.)

Using these 2 pieces of information (the mean effect of different doses of blood pressure–lowering drugs and the reduction in blood pressure that is required for that individual), the clinician can decide on the amount of therapy required for the individual before they start any blood pressure–lowering drugs. The drugs may still be introduced in a stepwise fashion whereby each drug is introduced one at a time starting at a low dose to ensure there are no adverse effects before therapy is escalated further. Monitoring blood pressure in the early period after starting treatment would only be needed if the patient began to experience adverse effects from therapy that might be attributable to hypotension. In this manner, treatment targets will be met more quickly, clinical benefits will be maximized, and inappropriate cessation of treatment will be averted. Although blood pressure monitoring to check that treatment is working would not be necessary, it may still be advisable to schedule clinic visits after starting therapy to check for adverse events and promote adherence, as well as to reinforce the patient-doctor relationship.

Longer-term blood pressure monitoring is likely to still be needed to detect the upward drift in blood pressure that occurs with aging (and the consequent need for escalation in treatment). However, recent research suggests that this too may be done much less frequently than is current practice. Long-term monitoring of blood pressure is probably best done at intervals of years rather than months to detect true changes in individual blood pressure against the background of random fluctuations.[20]

The trial participants in the current analysis were at high risk of a clinical event, and most were on other blood pressure–lowering drugs before starting the ACE inhibitor trial. It is possible that the true between-person variation in the effects of ACE inhibitors may differ in a lower-risk population, where an ACE inhibitor is the first-line drug. Similarly, the true between-person variation in the effects of ACE inhibitors may differ from that of other blood pressure–lowering drugs, such as diuretics, calcium channel blockers, β-blockers, and angiotensin II receptor antagonists. However, we may assume that the large within-person day-to-day variation in blood pressure that we found in this study is similar to that of most populations started on a drug to lower blood pressure. Indeed, our estimates are likely to be best-case scenarios, because blood pressure measurements made in the setting of clinical trials probably have less within-person variation than measurements made in clinical practice. Both high- and low-risk patients started on any blood pressure–lowering drug are likely to need an unfeasibly large number of blood pressure measurements to be taken if real treatment effects are to be disaggregated from the background day-to-day within person variation.

Perspectives

We found evidence of small between-person variations in the effects of ACE inhibitors on blood pressure, but the capacity for response monitoring practices to detect them is negligible. Effects of the drug in the individual are simply swamped by the usual within-person variation of blood pressure. This

raises fundamental questions about the value of current widely recommended strategies for blood pressure monitoring. Monitoring consumes considerable time for both the patient and the healthcare provider and probably adds little value. A simple alternative approach is to decide on the individual patient's therapy requirements before any drugs are started using the mean treatment effects observed in randomized trials. Monitoring blood pressure in the early period after starting treatment with an ACE inhibitor–based regimen is more likely to mislead than to inform about the efficacy of the treatment and should be avoided.

Sources of Funding

We have received funding from the Australian National Health and Medical Research Council (Public Health Postgraduate Scholarship No. 457212 and Program grants 402764 and 358395). European Trial on Reduction of Cardiac Events With Peridopril in Stable Coronary Artery Disease was funded by Servier, France. Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation was funded by grants from the National Health and Medical Research Council of Australia and Servier. Perindopril Protection against Recurrent Stroke Study was funded by grants from the Health Research Council of New Zealand, the National Health and Medical Research Council of Australia, and Servier. The Prevention of Renal and Vascular Endstage Disease Intervention Trial was funded by grants from the Dutch Kidney Foundation, The Netherlands Heart Foundation, and Bristol-Myers Squibb. Prevention of Atherosclerosis with Ramipril was funded by grants from the Health Research Council of New Zealand and Hoechst AG. The Bergamo Nephrologic Diabetes Complications Trial was partially funded by Abbott GmbH & Co. The Simvastatin/Enalapril Coronary Atherosclerosis Trial was funded by grants from the Medical Research Council of Canada and Merck Frosst Canada Inc.

Disclosures

B.C.N. received consultant fees from Pfizer, Roche, and Takeda; lecture fees from Amgen, AstraZeneca, GlaxoSmithKline, Pfizer, Roche, Sanofi Aventis, Servier, and Tanabe; and research support from Johnson & Johnson, Merck Schring Plough, Servier, and United Healthcare Group. W.J.R. received consulting fees from Pfizer, Novartis CV Therapeutics, and Servier and lecture fees from Daiichi-Sankyo, Takeda, Tanabe-Mistubishi, CV Therapeutics, and Servier. K.M.F. received honoraria and consultant fees from Servier Laboratories. G.R.'s institution received grants from Amgen and Abbot and consultant fees from Amgen, Abbott, and Astra Zeneca. S.M. received a research grant from Hoechst AG. K.K.T. received research grants and lecture fees from Boehringer Ingelheim.

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