

**Effects of blood pressure lowering on cardiovascular events, in the context of regression to the mean: a systematic review of randomized trials**

Abdul Salam, Emily Atkins, Johan Sundstro¨ m, Yoichiro Hirakawa, Dena Eftehad, Connor Emdin, Bruce Neal, Mark Woodward, John Chalmers, Eivind Berge, Salim Yusuf, Kazem Rahimi, and Anthony Rodgers, on behalf of the Blood Pressure Lowering Treatment Trialists’ Collaboration

**Objective:** To assess the clinical relevance of regression to the mean for clinical trials and clinical practice.

**Methods:** MEDLINE was searched until February 2018 for randomized trials of BP lowering with over 1000 patient-years follow-up per group. We estimated baseline mean BP, follow-up mean (usual) BP amongst patients grouped by 10 mmHg strata of baseline BP, and assessed effects of BP lowering on coronary heart disease (CHD) and stroke according to these BP levels.

**Results:** Eighty-six trials (349,488 participants), with mean follow-up of 3.7 years, were included. Most mean BP change was because of regression to the mean rather than treatment. At high baseline BP levels, even after rigorous hypertension diagnosis, downwards regression to the mean caused much of the fall in BP. At low baseline BP levels, upwards regression to the mean increased BP levels, even in treatment groups. Overall, a BP reduction of 6/3 mmHg lowered CHD by 14% (95% CI 11–17%) and stroke by 18% (15–22%), and these treatment effects occurred at follow-up BP levels much closer to the mean than baseline BP levels. In particular, more evidence was available in the SBP 130–139 mmHg range than any other range. Benefits were apparent in numerous high-risk patient groups with baseline mean SBP less than 140 mmHg.

**Conclusion:** Clinical practice should focus less on pretreatment BP levels, which rarely predict future untreated BP levels or rule out capacity to benefit from BP lowering in high cardiovascular risk patients. Instead, focus should be on prompt, empirical treatment to maintain lower BP for those with high BP and/or high risk.

**INTRODUCTION**

The intense interest in levels of blood pressure (BP) at which to initiate or intensify treatment has, to date, largely focused on baseline BP levels. However, BP is highly variable, fluctuating by time of day, from day to day and by season [1–3]. Therefore, like all physiological factors with intrinsic variability, BP exhibits regression to the mean [1,4,5]. If a patient has a high or low BP at any particular time, it is likely that average ‘usual’ BP in the past was closer to the mean and in the future will also be closer to the mean. This mean value for adults with cardiovascular risk factors is typically in the SBP 130–139 mmHg range [6]. Regression to the mean has two important implications for clinical practice and clinical trials. First, when initial BP is high or low, some of the BP change seen after initiating treatment will be because of regression to the mean rather than treatment. Second, when considering the question ‘to what BP range do the treatment effects in this clinical trial apply?’ the control group usual (follow-up mean) BP is more relevant than baseline BP, and the two measures will be systematically different if baseline BP is high or low.

No previous systematic reviews have quantified the contribution of regression to the mean to long-term BP changes in clinical trials, nor assessed treatment effect by control group usual BP. We, therefore, conducted a systematic review of all relevant randomized controlled trials (RCTs) of BP lowering in adults to assess baseline and usual BP levels and effects of BP lowering on stroke and coronary heart disease (CHD) according to these BP levels.
trials, frequency distributions were plotted for baseline and BP was estimated for each baseline BP strata. For BPLTTC to the same strata according to mean trial baseline BP. Usual baseline SBP and DBP and non-BPLTTC trials were allocated IPD from BPLTTC trials were divided into 10 mmHg strata of mean baseline and usual BP.

Statistical analysis

Outcomes were incidence of CHD and stroke according to outcomes were measured for antihypertensive agents, blood pressure/drug effects, randomized trials or meta-analyses, without language restrictions. Bibliographies of relevant publications were hand-searched to identify relevant publications.

Study selection

Eligible studies were RCTs of BP-lowering drugs, with a minimum of 1000 patient-years of follow-up in each randomized group and reported cardiovascular events. Trials broadly fell into three categories: hypertension trials: treatment vs. control (which was placebo in all but two trials [8,9] with no treatment) among patients who all initially had hypertension, variously defined open BP trials: treatment vs. control (which was placebo in all trials) among patients with a wide range of baseline BP values, either no BP entry criteria or exclusion only of people with high and/or low baseline BP (NB: this included trials in which investigators did not consider BP lowering to be the main mechanism of action); and more vs. less trials: comparisons of different BP-lowering targets (e.g. the HOT trial [10]) or intensities (e.g. the HDFP trial [11]), mostly among patients with hypertension at baseline. Head-to-head comparison of different drug classes were excluded, as were trials of dual renin–angiotensin–aldosterone system blockade (angiotensin receptor blockers added to angiotensin-converting enzyme (ACE) inhibitors, or vice versa; renin inhibitors or mineralocorticoid antagonists added to angiotensin receptor blockers or ACE-inhibitors), which do not lower BP appreciably and are now contraindicated in most or all patient groups. We included trials from the first cycle of the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) [12] as well as others (non-BPLTTC trials).

Data extraction and quality assessment

Individual participant data (IPD) was obtained for BPLTTC trials. For other trials, data extraction was conducted by two researchers (D.E. and C.E.) as outlined previously [7]. Usual BP was calculated directly for BPLTTC trials. Usual BP values for non-BPLTTC trials were extracted by two additional researchers (A.S. and E.A.). If not reported directly, this was estimated from published graphics of BP levels over time using the webplot digitizer application [13] (http://arohatgi.info/WebPlotDigitizer/). Finally, if not available from these sources, it was taken as the BP level at end of follow-up. Risk of bias was assessed using Cochrane collaboration’s risk of bias tool [14].

Outcome measures

Outcomes were incidence of CHD and stroke according to mean baseline and usual BP.

Baseline blood pressure, usual blood pressure and regression to the mean

For the 86 trials included, overall baseline mean SBP/DBP was 146/85 mmHg, usual BP in intervention and control group was 134/78 and 140/82 mmHg, respectively (Supplementary Table S2a, and Figure S1, http://links.lww.com/HJH/B37). Of these, 16 (63,923 participants) were hypertension trials; 56 (221,276 participants) were open BP trials; and 14 (64,289 participants) were more vs. less trials. Four studies (Supplementary references 12, 21, 22, 57, 59) were judged to be of unclear risk of bias and the remaining 82 trials were judged to have low risk of bias. The overall mean age at baseline was 62 years, 54% were women and mean follow-up period was 3.7 years. Average age at cardiovascular event was available for the BPLTTC trials only, and was 70 years. Overall, 14,421 CHD events and 7833 stroke events were synthesized in the meta-analysis.

RESULTS

Description of included studies and participants

In total, 86 eligible trials (349,488 participants) were included in the meta-analysis, of which 14 (66,513 participants, 19% of total participants) were BPLTTC trials (Supplementary Table S2a, and Figure S1, http://links.lww.com/HJH/B37). Of these, 16 (63,923 participants) were hypertension trials; 56 (221,276 participants) were open BP trials; and 14 (64,289 participants) were more vs. less trials. Four studies (Supplementary references 12, 21, 22, 57, 59) were judged to be of unclear risk of bias and the remaining 82 trials were judged to have low risk of bias. The overall mean age at baseline was 62 years, 54% were women and mean follow-up period was 3.7 years. Average age at cardiovascular event was available for the BPLTTC trials only, and was 70 years. Overall, 14,421 CHD events and 7833 stroke events were synthesized in the meta-analysis.

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The results were closely consistent between BPLTTC IPD estimates derived from 10 mmHg strata within trials, compared with non-BPLTTC estimates based on overall mean BP in a trial (Supplementary Table S3, http://links.lww.com/HJH/B37).

In participants with high or low baseline BP, the effects of regression to the mean were at least as great as the effects of active treatment (Supplementary Table S3, http://links.lww.com/HJH/B37). For example, in the treatment vs. control trials in the baseline SBP 150–159 mmHg stratum, mean baseline SBP was 155 mmHg, whereas control vs. treatment group usual SBP was 145 vs. 140 mmHg, respectively. Thus, of the 15 mmHg drop in the active group, 10 mmHg was because of regression to the mean. For lower baseline BP levels, upwards regression to the mean tended to be greater than the effects of treatment downwards – for example, in treatment vs. control trials in the baseline SBP strata of 120–129 mmHg, baseline mean SBP was 124 mmHg, and the treatment and control group usual SBP was 125 and 129 mmHg, respectively. Therefore, BP levels on average hardly changed in the treatment group, as treatment counter-balanced the effects of upwards regression to the mean.

Regression to the mean was still evident in trials that sought to confirm a diagnosis of hypertension at baseline with a BP screening phase (Fig. 2) [16–23]. In these trials, eligible participants had to meet hypertension criteria on all prerandomization screening assessments, which were typically 2–3 visits or placebo run-ins of up to 12 weeks (Supplementary Table S2b, http://links.lww.com/HJH/B37). Nonetheless, BP fell by 12 mmHg in the placebo group over the first year, which was half of the 24 mmHg drop seen in the active treatment group. Regression to the mean was reduced, although still substantial with even more repeated measures, being evident if ‘baseline’ BP was taken as the average of all measures over a 1-year period (Supplementary Figure S2, http://links.lww.com/HJH/B37). For example, among placebo group patients whose average first year BP were in the at least 160 mmHg and less than 120 mmHg range the means at baseline were 170 and 114 mmHg, respectively, whereas at 4 years, they were 157 and 123 mmHg, respectively.

The distributions of BP at baseline and follow-up for BPLTTC trials, by type of trial (hypertension, open BP and more vs. less – Supplementary Figure S5, http://links.lww.com/HJH/B37) help assess the question ‘what BP levels was the intervention treatment compared against?’ Although all hypertension trials had baseline SBP greater than 160 mmHg with a marked skew to the right, the control group usual SBP in these trials (i.e. the BP that intervention was compared against for the majority of follow-up) was normally distributed with a mean at around 160 mmHg, that is, usual SBP was below entry threshold BP for around half of the participants during the course of follow-up. The distributions of control group usual SBP were the same shape in all three sets of trials and overlapped considerably, providing support for pooling the sets of trials. There was a concentration of follow-up at BP levels near the mean: 139 (40%) of participants were in trials or subgroups with control group usual SBP in the 130–139 mmHg range, compared with only 56 503 (16%) at baseline.
Treatment effects on coronary heart disease and stroke, by blood pressure level

Overall the BP difference between treatment and control groups was 6/3 mmHg, conferring a 14% (95% CI 11–17%) CHD reduction and 18% (95% CI 14–21%) stroke reduction (Supplementary Table S4, http://links.lww.com/HJH/B37). Figure 3 shows these results for each baseline BP stratum, with treatment effects plotted at control group usual SBP.
levels, that is, the average BP against which treatment was compared. The reductions in stroke and CHD were separately significant for most subgroups and occurred at levels that were generally closer to the 130–139 mmHg range. Consistent reductions in CHD and stroke for narrower bands of control usual SBP, including each 2.5 mmHg band in the 130–139 mmHg range, are shown in Supplementary Figure S6, http://links.lww.com/HJH/B37.

There was no evidence that the proportional reductions in CHD and stroke were different in BPLTTC vs. non-BPLTTC trials, those with and without vascular disease, or by type of trial, with the exception of a larger effect on stroke in the hypertension trials, presumably driven by the greater BP reduction seen in those trials (Supplementary Table S4, http://links.lww.com/HJH/B37). There was some evidence of lesser proportional reductions in CHD and stroke (heterogeneity $P = 0.02$ and $P = 0.03$, respectively) in trials in which all participants had diabetes compared with other trials, despite similar average BP reductions.

There was evidence that trials with larger BP reduction with treatment vs. control had larger reductions in both CHD and stroke ($P = 0.01$).

For six different patient subgroups, regression to the mean upwards was seen in all patient subgroups for the baseline SBP less than 120 mmHg group, and for five out of six patient subgroups, regression to the mean upwards was seen for the baseline SBP 120–129 mmHg stratum (Fig. 4). The size of this regression to the mean effect was generally larger than the treatment effect, such that mean BP increased in treatment groups, and rose even further in control groups. For the baseline SBP 130–139 mmHg stratum, where most population mean levels lie, control group usual BP levels remained about constant for all patient subgroups. A combined outcome of CHD or stroke was assessed to maximize power, and for all participants with baseline SBP less than 140 mmHg, this was reduced by 16% (95% CI 12–19%) overall (Fig. 4). There were separately significant and similar-sized reductions in combined CHD

![FIGURE 4 Treatment effects on blood pressure and coronary heart disease and stroke, for different patient subgroups with baseline SBP under 140 mmHg. Groups were defined according to whether all trial participants had cerebrovascular disease (i.e. previous stroke or Transient ischaemic attack (TIA), recent myocardial infarction (MI), stable CHD, heart failure or left ventricular dysfunction (LVD) and all other trials).](image-url)
DISCUSSION

Regression to the mean has played a substantial role in determining achieved BP levels in trials of BP lowering, and was still apparent after extensive repeat measures over weeks and months. Overall, a 6 mmHg reduction in SBP reduced CHD by 14% and stroke by 18%, which was closely consistent with epidemiological associations (6 mmHg lower usual SBP is associated with 14% lower CHD risk and 19% lower stroke risk in people aged 70–79 years) [24]. Benefits were apparent in numerous high-risk patient groups with baseline SBP less than 140 mmHg, with more evidence of benefit in the SBP 150–139 mmHg group than for any other.

This systematic review benefitted from a large sample size, with over 14,000 CHD and 7000 stroke events observed overall. The IPD provided much more information than has previously been available at the lowest BP levels and hence the most reliable assessment to date against the existence of a J-curve association for CHD or stroke at lower BP levels. Grouping trials by control group usual BP provided a reliable assessment of treatment effects at different BP levels, as randomization was preserved. The separate analysis of the treatment effects on CHD and stroke events allowed direct comparison with associations in observational studies [1,24] and avoided heterogeneity because of variable makeup of composite outcomes such as major vascular events by BP level or patient group. The broad inclusion of trials reduced type II error [25], and allowed results to be compared and contrasted across major groups of participants.

Limitations of this review include lack of data available from all trials to assess how much BP change in control groups was because of regression to the mean and how much was because of treatment changes. However, detailed analyses of one trial (Fig. 1) showed that treatment changes could not have played much role in changing control group BP; rather the symmetrical patterns in BP change could only plausibly be explained by upwards and downwards regression to the mean. No trials in this review included randomization between no treatment and placebo, but a review of such trials has shown similar BP drops with no treatment and placebo in hypertension [26]. One other area that could be explored in future is the assessment of effects of BP-lowering drugs in the presence of different concomitant treatments given for other cardiovascular risk factors. Another important limitation of the review was the lack of IPD for all trials. This prevented more detailed analysis of treatment effects across levels of baseline and usual BP, by major patient groups, by types of intervention, and by the presence of different concomitant treatments. For example, comparisons of trials in which all participants had diabetes with trials in which some or none had diabetes, will tend to underestimate any treatment modification by diabetic status. However, systematic reviews including more than 100 trials and involving analysis across multiple patient groups [7,27] have shown remarkably consistent effects of different BP-lowering drugs on most outcomes across most patient groups. Several dimensions of BP treatment might contribute to heterogeneity (e.g. reduction of central BP [28], BP variability [29], particular benefits of calcium channel blockers on stroke, or beta-blockers on CHD [27]), but the size of these effects are typically much smaller than the size of treatment vs. no treatment. This review focused only on CHD and stroke outcomes and it remains a possibility that BP-dependent benefits have little importance for these outcomes below 140 mmHg and are instead replaced by other mechanisms that confer a similar degree of benefit. However, the close consistency of observed event reductions with epidemiologically expected effects [24] suggests that most or all of the reductions in CHD and stroke observed in this review can be attributed to BP lowering per se. Preferential use of drug classes used in previous trials ensures the benefits accrue, whatever the mechanism.

These results have several important implications for clinical practice, with ramifications for each step of the current paradigm of attempting to establish a baseline BP before treatment, treating only those with BP above 140/90 mmHg and using posttreatment changes in BP levels to estimate individual patient response to drugs and doses. First, pretreatment usual BP levels are essentially unknowable for patients with hypertension in the modern era, as regression to the mean continues for many months [1,30] and untreated periods of this duration are clinically unacceptable. The average of BP measures taken over just a few weeks or months will overestimate future untreated BP for people with hypertension. Baseline BP cannot generally be considered the best estimate of future untreated BP level, from which treatment efficacy can be judged, now no matter how it is measured. Further, in a separate article [31], we demonstrate regression to the mean even with ambulatory BP monitoring. Therefore, as past trials showed unequivocal benefits of treating high BP, whether based on single or repeated measures, treatment should in general be initiated promptly among patients with high BP. Second, as it is impossible clinically to differentiate BP changes because of treatment from those because of regression to the mean, guidelines should emphasize the inability of follow-up BP measures to reliably assess individual treatment response. Instead treatment strategies should be more empirical, that is, driven by the results from randomized trials and less by estimated individual BP responses. For example, a clinician initiating hypertension treatment with low-dose monotherapy and then increasing the dose could falsely conclude that a large BP drop confirmed that patient responded well to that drug or benefitted substantially from a dosage increase. Placebo-controlled trials show neither is likely [32]. 'Tailwind' effects occur if initial BP is high and attributing all BP reduction after initiating hypertension...
treatment to treatment will generally overestimate efficacy. Conversely, 'headwind' effects when initial BP is below average can mean BP-lowering therapy does not lower BP levels. It would be easy to falsely conclude treatment was ineffective, or operated through non-BP-dependent mechanisms. These tailwind and headwind effects are average effects over time in groups. Intra-individual variability makes it even harder to reliably determine individual treatment response (or even whether patients are currently taking any treatment), given the consequent signal-to-noise ratio [33,34]. Third, these results reinforce and extend previous analyses [7,27] showing that the benefits of BP lowering extend considerably below 140/90 mmHg, and RCTs do not indicate a ‘J-curve’ effect. Much of the evidence previously ascribed to the greater than 130–139 mmHg BP range is actually more clinically relevant to the 130–139 mmHg range, as so many control group trial participants had usual BP levels in that range, and their baseline BP levels were simply chance high assessments. The evidence in high-risk patients of greater benefits with greater BP lowering, including additional BP lowering below 140/90 mmHg [7,35], further indicates reappraisal of current treatment thresholds is required, and some [36,37] but not all [38] hypertension management guidelines have reflected this evidence. Evidence below the 140/90 mmHg level is almost entirely from trials in high-risk patient groups. The most appropriate strategy to generalize such evidence is controversial. Some may require evidence for each patient subgroup in each BP subgroup, whereas others will say the lack of heterogeneity in reduction of CHD and stroke across different patient groups indicates a broadly generalizable finding. At the least, these data suggest treatment should be considered for most patients with CHD or similarly high-risk whose usual BP is below 140 mmHg.

The foregoing implications for clinical practice should be included in future hypertension guidelines, which at present provide no guidance on the clinical implications of regression to the mean. In addition, to date hypertension guidelines have only based recommendations on trials in which all patients had hypertension at baseline and have generally implied that treatment effects are only relevant to entry BP criteria. A new approach is required – for example, a large number of RCTs have generated evidence relevant to the topical issue of whether or not there are benefits of treatment initiation or intensification among people with SBP in the 130–139 mmHg range. The overemphasis of baseline measures and arbitrary dichotomous BP criteria and restriction to ‘hypertension trials’ has led to large amounts of relevant randomized evidence being inappropriately excluded from past hypertension guidelines. The results also have relevance for clinical trials – control groups will continue to be needed as some degree of regression to the mean is inevitable. Regression to the mean is less but still substantial following repeated measures, better office measures and ambulatory measures [31].

In conclusion, these results suggest reappraisal of each step of the current paradigm of attempting to establish a pretreatment baseline BP, treating only those with BP above 140/90 mmHg and attempting to determine individual response to therapy from measured BP changes [7,24,27,28,29,39,40]. The main focus should instead be on prompt treatment initiation and long-term management of lower BP levels among patients with high BP and/or high cardiovascular risk.

REFERENCES


