EFFECTS OF BLOOD PRESSURE LOWERING ON CARDIOVASCULAR EVENTS, IN THE CONTEXT OF REGRESSION TO THE MEAN: A SYSTEMATIC REVIEW OF RANDOMIZED TRIALS

Short title: Blood pressure lowering and regression to the mean

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Abstract

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

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 3.7 years, were included. Most mean BP change was due to 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 systolic BP (SBP) 130-139 mmHg range than any other range. Benefits were apparent in numerous high-risk patient groups with baseline mean SBP<140 mmHg.

Conclusion: Clinical practise should focus less on pre-treatment 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.

Keywords: Blood pressure; Regression to the mean; Antihypertensive therapy: Coronary Heart Disease; Stroke; Systematic review

Introduction

The intense interest in levels of blood pressure (BP) at which to initiate or intensify treatment has, to date, largely focussed 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 systolic BP (SBP) 130-139 mmHg range [6]. Regression to the mean has two important implications for clinical practise and clinical trials. First, when initial BP is high or low, some of the BP change seen after initiating treatment will be due to 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.

Methods

Data Sources and Searches

The search strategy for the review was outlined in full in a previous publication [7], and it was updated for this review (*Supplementary Table S1*). In brief, MEDLINE was searched from January 1966 to February 2018 using keywords and Medical Subject Headings for anti-hypertensive 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: (i) hypertension trials: treatment vs. control (which was placebo in all but 2 trials [8,9] with no treatment) among patients who all initially had hypertension, variously defined (ii) 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 (iii) 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 (DE, CE) 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 (AS, EA). 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.

Statistical Analysis

IPD from BPLTTC trials were divided into 10 mmHg strata of baseline SBP and diastolic BP (DBP) and non-BPLTTC trials were allocated to the same strata according to mean trial baseline BP. Usual BP was estimated for each baseline BP strata. For BPLTCC trials, frequency distributions were plotted for baseline and usual BP levels, by type of trial. Overall relative risks and 95% confidence intervals (CIs) for CHD and stroke outcomes were calculated using inverse variance weighted fixed-effect meta-analyses to avoid small study bias.[15] Heterogeneity was quantified by the I^2 statistic and tested using Cochrane's *Q* statistic, which was also used to test for subgroup interactions. All p-values were two-tailed at 5% significance level. Analyses were performed using Comprehensive Meta-analysis (V3, Biostat Inc, Englewood, USA).

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*). 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, 34% were female 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.

Baseline BP, Usual BP 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 S2b*). Substantial downwards regression to the mean was observed for high baseline BP and upwards regression to the mean was observed for low baseline BP. This effect is shown in detail for one trial in *Figure 1,* which shows that patients with high initial BP levels tended to have a large fall in BP in the first 3-6 months, which was greater in the treatment than in the placebo group. Conversely, patients with low initial BP levels tended to have an increase in BP in the first 3-6 months in the placebo group while BP levels remained approximately constant in the treatment group (i.e. active treatment counterbalanced upwards regression to the mean). Most regression to the mean occurred within 3-6 months, but for those with the most extreme baseline BP levels, regression to the mean continued for several years. Drop-out from study treatment and drop-in of non-study BP treatment played little role in explaining the patterns: regression to the mean occurred mostly over the first 3-6 months, while drop-in and drop-out rates were particularly low during this period (*Figure 1*). Also, the frequency distribution of BP did not change through follow-up in the placebo group: patients with high initial BP that dropped after baseline were replaced in equal number by patients whose initial BP was not high but cycled upwards.

Similar patterns of downwards and upwards regression to the mean were seen for other trials

(*Supplementary Figure S2, S3 and S4*). The results were closely consistent between BPLTTC IPD estimates derived from 10 mmHg strata within trials, compared to non-BPLTTC estimates based on overall mean BP in a trial (*Supplementary Table S3*).

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*). For example, in the treatment vs. control trials in the baseline SBP 150-159 mmHg stratum, mean baseline SBP was 155 mmHg, while control vs. treatment group usual SBP was 145 mmHg vs. 140 mmHg, respectively. Thus, of the 15 mmHg drop in the active group, 10 mmHg was due to 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, since treatment counterbalanced 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 (*Figure 2*) [16-23]. In these trials eligible participants had to meet hypertension criteria on all pre-randomization screening assessments, which were typically 2-3 visits or placebo run-ins of up to 12 weeks (*Supplementary Table S2b*). Nonetheless, BP fell by 12mmHg 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).* For example, among placebo group patients whose average first year BP were in the ≥160 mmHg and <120 mmHg range the means at baseline were 170 mmHg and 114 mmHg respectively,

while at 4 years they were 157 mmHg 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*) help assess the question "what BP levels was the intervention treatment compared against?" Although all hypertension trials had baseline SBP>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 i.e. 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: 139,405 (40%) of participants were in trials or subgroups with control group usual SBP in the 130-139 range, compared to only 56,503 (16%) at baseline.

Treatment Effects on CHD and Stroke, by BP level

Overall the BP difference between treatment and control groups was 6/3 mmHg, conferring a 14% (95% CI 11% to 17%) CHD reduction and 18% (95% CI 14% to 21%) stroke reduction (*Supplementary Table S4*). *Figure 3* shows these results for each baseline BP stratum, with treatment effects plotted at control group usual SBP levels, i.e. 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*.

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*). 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 to 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<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 (*Figure 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 maximise power, and for all participants with baseline SBP <140 mm Hg this was reduced by 16% (95% CI 12 % to 19%) overall (*Figure 4*). There were separately significant and similar-sized reductions in combined CHD and stroke for each of the <120, 120-129 and 130-139 mmHg baseline SBP strata. Although the baseline SBP values differed considerably, the usual SBP values of these groups differed little (127, 129 and 134 mmHg respectively). Within each stratum there was only significant heterogeneity in treatment effect across subgroups in the 130-139 mmHg baseline BP strata (p=0.02). However, in the baseline SBP<120 mmHg stratum, the large majority of events occurred in participants with CHD or heart failure and so there was particularly limited power to assess heterogeneity compared to other patient groups.

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<140 mmHg, with more evidence of benefit in the SBP 130-139 mmHg group than for any other.

This systematic review benefitted from a large sample size, with over 14,000 CHD and 7,000 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, since 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 due to 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 due to regression to the mean and how much was due to treatment changes. However, detailed analyses of one trial (Figure 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 randomisation 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 focussed 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 practise, 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 post-treatment changes in BP levels to estimate individual patient response to drugs and doses. First, pre-treatment usual BP levels are essentially unknowable for patients with hypertension in the modern era, since 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 paper (J Hypertens 'in press'[31]), we demonstrate regression to the mean even with ambulatory BP monitoring. Therefore, since 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, since it is impossible clinically to differentiate BP changes due to treatment from those due to regression to the mean, guidelines should emphasise the inability of follow-up BP measures to reliably assess individual treatment response. Instead treatment strategies should be more empirical i.e. 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 >140/90 mmHg BP range (based on eligibility criteria and baseline levels) is actually more clinically relevant to the 130-139 mmHg range, since 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 generalise such evidence is controversial. Some may require evidence for each patient subgroup in each BP subgroup, while others will say the lack of heterogeneity in reduction of CHD and stroke across different patient groups indicates a broadly generalisable 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 practise 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. The over-emphasis 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.

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

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Figure Legends

Figure 1

Mean BP over time in treatment and control groups in the PROGRESS trial. In the top panel, mean SBP levels at baseline and for each follow-up visit are plotted for strata defined by baseline SBP, for treatment and placebo groups separately. In the bottom panel, use of study treatment and non-study BP lowering treatment is shown by baseline SBP levels over time, for treatment and control groups (there was little difference in adherence to study treatment by baseline BP levels and therefore these lines are indistinguishable).

Figure 2

Mean SBP levels over time are plotted for hypertension trials that employed screening in which all patients had to meet hypertension criteria before randomization (as outlined in Supplementary Table S1), by treatment and placebo groups.

Figure 3

This illustration depicts mean baseline and follow-up BP level for each baseline BP stratum and treatment effects on CHD and stroke. The first vertical panel shows the trajectory of mean BP from baseline to usual levels, for each baseline BP group and for treatment and control groups. The second and third panels show the treatment effects on CHD and stroke, respectively, for each group defined by baseline BP and plotted at control usual BP i.e. the mean BP against which treatment was compared during follow-up. Each relative risk is represented by a square and each 95% confidence intervals by a horizontal line. For the DBP 90-99 mmHg group, treatment effects are plotted at 86 mmHg rather than 87 mmHg so as to not overlap the treatment effect estimates for the >100 mmHg group. The mean control DBP levels for both groups were 87 mmHg. Stroke treatment effects for <120 mmHg SBP and <70 mmHg DBP were 0.68 (0.41-1.15) and 0.96 (0.68-1.35), respectively and are not plotted since <20 events observed.

Figure 4

Treatment effects on BP and CHD 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 TIA), recent myocardial infarction (MI), stable CHD, heart failure or left ventricular dysfunction (LVD) and all other trials.