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ORIGINAL ARTICLE

Apparent effect on blood pressure is only partly responsible for the risk reduction due to antihypertensive treatments

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ABSTRACT

The mechanism of risk reduction obtained by blood pressure-lowering pharmacological treatment remains unclear. We explored the amount of risk reduction attributable to the apparent effect of antihypertensive medicines on blood pressure by using the capture approach. Five randomized, placebo or nil controlled trials with a total of 28 997 subjects and 1935 cardiovascular fatal or non-fatal events from the INDANA database met the eligibility criteria. Computations were performed on the original individual records using multiple Cox's proportional hazard regression models designed for meeting the assumed treatment mode of action and comparing relevant assumptions. For coronary event, the results are inconclusive essentially because the risk reduction is mild. However, for stroke the risk reduction adjusted for baseline risk factors is 34% ($P < 0.0001$). The part explained by the effect of treatment on systolic blood pressure is 49% of this reduction, with 95% confidence interval not including 100%. This result suggests that the apparent effect on blood pressure is not the only cause of stroke risk reduction in hypertensive subjects submitted to an antihypertensive medicine.

INTRODUCTION

Hypertension, i.e. elevated systolic (SBP) and/or diastolic blood pressure (DBP), was recognized many decades ago as one of the leading predictors of cardiovascular mortality and morbidity: stroke, myocardial infarction and sudden death. A reduction of cardiovascular risk has been clearly demonstrated, both in randomized clinical trials and in meta-analyses, with several classes of blood pressure-lowering drugs with different mechanisms of action, e.g. beta-blockers, diuretics and calcium channel blockers. This experimental evidence affirms that there is a causal relationship between the antihypertensive interventions and risk reduction. However, the mechanism of such risk reduction has not been determined, nor the extent to which the decrease in blood pressure induced by antihypertensive drugs itself contributes to the risk reduction.

Considerations about the relationships between antihypertensive therapies, blood pressure on treatment and risk reduction turned to be rather different according to the question one strives to answer: are the blood pressure values after 1 or 2 months of treatment a 'good' surrogate for assessing the benefit of new antihypertensive agents? Is a short-term decrease of blood pressure in a patient recently treated with an antihypertensive regimen predictive of a clinically significant reduction of his/her risk of cardiovascular morbidity? What is the amount of risk reduction observed with antihypertensive therapies 'explained' by their effect on blood pressure?

The last two questions cover quite different issues. For instance, a mechanistic one: is lowering the intra-arterial pressure, systolic, diastolic or both, the only cause or one of the causes of cardiovascular risk reduction observed in randomized trials of blood pressure-lowering regimens? Or a purely phenomenological issue: does the apparent or observed blood pressure decrease caused by blood pressure-lowering regimens explain the decrease in cardiovascular risk? The last two questions differ because of the blood pressure measured through cuff and mercury devices are quite imperfect measures of the true intra-arterial pressure. The mechanistic question is almost impossible to explore directly. The phenomenological question is easier to address. Its interest lies on its central position regarding all the other issues. If the apparent decrease of blood pressure caused by treatment explains all the risk reduction, then a positive answer to all other questions becomes possible.

This study explores the extent to which the apparent effect on blood pressure explains the risk reduction in hypertensive subjects. We compiled a database of individual patient records from several randomized controlled clinical trials that have addressed the potential for risk reduction in hypertensive subjects and used an approach proposed by Freedman, applied to the treatment of AIDS [1]. We modelled the effect on risk of stroke and of coronary heart disease (CHD) both with and without taking into account the treatment effect on blood pressure.

METHODS

The INDANA database comprises the individual records of 53 228 patients in 11 major randomized controlled trials designed to assess the preventive value of antihypertensive treatment on cardiovascular risk [2–12]. Six of these trials were excluded from our analysis, MRFIT [2] because only death was recorded, HDFP [6] because blood pressure values were available only at 2 and 5 years of follow-up, EWPHE [4] and the Australian trial [12] because only the first event to occur was recorded, the VA-NHLBI [11] trial because of the small number of patients and the SHEP Pilot study [10] because of the lack of blood pressure follow-up data needed for the analysis. The retained data from five trials comprise 28 997 patients who experienced 1935 fatal or non-fatal cardiovascular events (see *Table I*) [3,5,7–9]. Details of the five trials are given elsewhere [13]. The outcomes explored were stroke, both fatal and non-fatal (excluding transient ischaemic attack) and major coronary events (CHD, which includes fatal and non-fatal myocardial infarction and sudden death), as defined previously [13]. We obtained blood pressure data from the database at baseline, 6 months and 1 year. Although most of the difference between treated and control patients is seen within 6 months, we examined two series of models, using 6-month or 1-year blood pressure values. We focussed on SBP as in multivariate analyses in the INDANA database it was more consistently and strongly associated with risk, both for stroke and CHD, than diastolic pressure [14].

To model the treatment effect on risk as expressed by the risk reduction, we used a Cox's proportional hazards regression model [15]. We followed the approach suggested by Prentice [16], modified by Freedman et al. and Buyse and Molenberghs [17,18]. The principle consists in estimating how much of the treatment effect on the target variable (here the risk) is 'captured' by the treatment effect on the explicative variable (here the blood pressure) when the latter is combined in the appropriate

Table I Trials retained to explore the part of risk reduction attributable to treatment effect on blood pressure.

Trial	Active treatment	Control	No. of subjects	Coronary disease	Stroke	No. of patients without event
COOPE [5]	Atenolol (+ bendrofluazide, then alpha-methyldopa if needed)	Nil	884	73	59	757
MRC1 [3]	Bendrofluazide or propranolol (+ alpha-methyldopa if needed)	Placebo or nil	17 354	456	169	16 736
MRC2 [9]	Hydrochlorothiazide and amiloride, or atenolol (+ nifedipine if needed)	Placebo	4396	287	235	3887
SHEP [7]	Chlortalidone (+ atenolol, then reserpine if needed)	Placebo	4736	245	262	4248
STOP [8,10]	Hydrochlorothiazide and amiloride, or atenolol, metoprolol or pindolol (then diuretic + beta-blocker if needed)	Placebo	1627	66	83	1479
Total			28 997	1127	808	27 107

model. If the capture is 100%, this means the effect on the explicative variable explains all the effect on the target variable. Patients who died before the blood pressure time points were not included in the analysis. Non-fatal events that occurred before the same time points were not taken into account. A sequence of three models was used. All models were adjusted for those baseline variables which were significantly associated with risk in the database: age, gender, baseline blood cholesterol, and smoking. Treatment activity on blood pressure has been accounted for through two different approaches. One assumed the effect is carried by a fall in blood pressure, the other that only the pressure reached on treatment matters. Models meeting the former approach adjust the risk reduction on the baseline SBP. Models meeting the later approach were not adjusted on baseline blood pressure.

In all cases, part of risk reduction attributable to treatment effect on blood pressure was obtained by comparing model 1 and model 2 or model 3. Model 1 measured the effect of the treatment unadjusted for on-treatment SBP. In model 2 we adjusted for the on-treatment level in SBP or DBP at 6 or 12 months (adjusted results), and in model 3 we added an interaction between the effect of the treatment and the change in blood pressure at 6 or 12 months. Parameter estimates of the treatment effect conditional on the decrease of blood pressure achieved at 6 or 12 months (models 2 or 3) were compared with those unadjusted on blood pressure (model 1). The part of the risk reduction attributable to the treatment effect on blood pressure (proportion explained, PE) was computed by subtracting the latter estimates from the former and dividing by the latter. PE values were computed with corrected estimates. The effect of blood pressure measurement errors on the treatment effect estimates was taken into account by multiplying the naive parameter estimates by a correcting coefficient [19]. This coefficient allows to account for the uncertainty of the values of blood pressure. It was estimated separately for each trial, using the repetition of blood pressure measurements at 6 months and 1 year. A PE <100% indicates that the apparent blood pressure effect of the treatment does not explain fully the risk reduction. The results are given with their standard error (SE). Bootstrap methods were used to calculate 95% confidence intervals (CIs) conditional on the effect of treatment [20]. The 2.5 and 97.5% percentiles of the distribution of 2000 re-samplings were used as the limits for these CIs.

RESULTS

The results based on 6-month SBP data are shown on *Table II*. Findings obtained with 1-year blood pressure measurements of SBP or without adjustment for baseline blood pressure are similar, and thus not shown. The interaction between the effect of the treatment and the change in blood pressure at 6 or 12 months was not statistically significant ($P = 0.21$ for CHD and $P = 0.73$ for stroke) and the coefficients for treatment and change in blood pressure in model 3 were almost the same as in model 2 without interaction. Thus, we used only models 1 and 2 to compute the part of risk reduction attributable to the treatment effect on blood pressure. The unadjusted parameter estimate of treatment effect for stroke was −0.53 (0.07), corresponding to a highly statistically significant treatment effect on the risk of stroke ($P < 0.0001$). The adjusted uncorrected overall treatment effect estimates was equal to −0.42 (0.08), and equal to −0.27 (0.12) after correction for measurement error. The corresponding hazard ratio (95% CI) were 0.68 (0.58–0.80) and 0.79 (0.63–0.94). Hence, because

Table II Parameter estimate of treatment effect (risk reduction) and proportion of the hazard reduction explained (proportion explained: PE) by the treatment effect on blood pressure at 6 months (all models are adjusted on age at baseline, gender, baseline SBP, baseline blood cholesterol, baseline smoking).

	Model 1 (unadjusted on 6-month SBP)		Model 2 (adjusted on 6-month SBP)			
	Parameter estimate (SE)	*P*	Uncorrected parameter estimate (SE)	*P*	Corrected[a] parameter estimate (SE)	PE (95% CI)
(1) Major CHD events, fatal and non-fatal	−0.11 (0.06)	0.07	−0.04 (0.07)	0.57	0.09 (0.09)	
(2) Stroke, fatal and non-fatal	−0.53 (0.07)	<0.0001	−0.42 (0.08)	<0.0001	−0.27 (0.12)	49% (15–88%)

[a]Corrected: correction for blood pressure determination uncertainty using an approximate coefficient [19].

of random error on the measurement of SBP, the naive SBP-adjusted treatment effect was overestimated by about 50% as compared with the corrected estimate. This latter estimate still indicates that conditionally on the blood pressure level achieved at 6 months, treatment reduces the risk of stroke by 21% (95% CI: 6–37). The PE is: 0.49 (95% CI: 0.15–0.88), indicating that for stroke the risk reduction is not fully explained by the decrease of blood pressure caused by the treatment. Actually, only 49% of the observed risk reduction is explained by the treatment effect on blood pressure. For CHD, the unadjusted treatment effect estimate was: −0.11 (0.06), $P = 0.07$. The uncorrected and corrected SBP-adjusted relative risks were 0.99 (0.88–1.12) and 1.12 (0.95–1.31) respectively. As the CHD risk reduction was not statistically significant, we do not present the value of PE, which is irrelevant.

DISCUSSION

These results show that the observed effect on blood pressure attributed to the antihypertensive treatment (either considered as the achieved level or the magnitude of blood pressure change from baseline) does not explain fully the risk reduction obtained with the treatment. The validity of the proof rests mainly on the accuracy of the estimate of the treatment effect on blood pressure. In turn, inaccuracy here has two dimensions, lack of precision and bias. The lack of precision was taken into account by correcting for measurement error. We accounted for the lack of precision of the blood pressure measurements by using the procedure proposed by Carrol et al. [19]. It remains that the correction is approximate and might result in an underestimation of the effect of uncertainty. However, the results for stroke are likely to be robust because of the value of the PE index (49%) is far from 100% and the upper limit of the CI well below 100%. Regarding bias, it is well established that cuff blood pressure is a biased measurement of the true physiological parameter, the intra-arterial pressure. However, this bias is likely to be the same, for a given individual, at baseline and at, say, 6 months of follow-up. More important, we did not aim at assessing the part of risk reduction explained by the treatment effect on true arterial blood pressure. Instead, we limit ourselves to the apparent decrease of blood pressure due to the treatment. The other causes of bias to consider are: placebo effect, regression to mean phenomenon and/or natural evolution of blood pressure that mimic or hide the true treatment effect. This bias was neutralized by the similar bias of the change in blood pressure in the control patients. Thus, because of the structure of the database – randomized treated and control cases – and of the structure of the models, the treatment effect on apparent blood pressure estimate is unbiased.

We recognize that using a single assessment of blood pressure at 6 months (or 12 months) limits the appraisal of the treatment effect on blood pressure. However, data on earlier blood pressure measurements were not available in several of our trials, which hampered the use of other summary statistics (such as the area under the curve). Although unlikely, it remains possible that a shorter time effect would be an additional determinant of the risk reduction.

The part explained by treatment effect on blood pressure values is not the same for CHD risk as for stroke (not shown). This suggests a difference in the mechanism of both types of event. Hints for a difference in the treatment mechanism of action against stroke and against CHD have been given by the identification of the time-dependent effect on the occurrence of each type of outcomes by estimating the hazard ratios [21].

Our computations showed no statistically significant interaction between treatments tested in the five trials on the relationship between blood pressure and risk of stroke. For instance, parameter estimates for 6-month blood pressure are 0.0072 (SE: 0.0036) and 0.0085 (SE: 0.0027) for active groups and controlled groups respectively. Our data suggest in addition that the blood pressure achieved on treatment (here after 6 months) is the value that matters for the part explained by the treatment effect on blood pressure.

MacMahon et al. [22] estimated the expected risk reduction from the specific parameters of the relationship between blood pressure and risk estimated through a meta-analysis of several large epidemiological studies. They compared the result, after correcting for the dilution bias due to the regression to the mean phenomenon, when they were applied to the average blood pressure difference due to treatment, with the observed risk reduction in a meta-analysis of available controlled clinical trials [22]. They concluded that the risk reduction observed for stroke corresponded to that expected from the epidemiological data, but this risk reduction was less than expected for CHD [23]. These findings apparently contradict our own results. However, Collins et al. [23] used summarized data from each trial, whereas our use of individual patient data is more powerful. In addition, we did not refer to data obtained from subjects in observational studies who are likely

to be different in terms of risk profile from those in randomized trials on whom the treatment effects have been computed.

Staessen et al. [24] showed that risk reduction was correlated with the observed differences in blood pressure between the experimental and reference groups in randomized clinical trials with blood pressure-lowering drugs, a finding which is not at variance with ours. However, they concluded that the risk reduction observed in randomized trials of drugs can be explained by blood pressure differences between randomized groups. Actually, the findings presented in their article do not support their conclusions, but on the contrary suggest that the risk reduction does not parallel the treatment effect on blood pressure. First, the significant meta-regressions (for stroke and for myocardial infarction), demonstrated a correlation between the risk reduction and the blood pressure differences between experimental and reference groups, a difference which is assumed to represent the experimental treatment effect on blood pressure over the reference treatment effect. A correlation does not mean causality, and tells us very little on the relationship between differences on blood pressure and differences in risk between the groups but that are statistically linked. Secondly, the shape of the relationship suggests that the relationship between the risk reduction and antihypertensive treatment effect on blood pressure is neither linear nor log-linear. This suggests a more complex relation than the authors have anticipated from their assumption that the demonstrated risk reduction is fully explained by the reduction of blood pressure.

A J-shaped relationship between DBP and risk was observed on total and cardiovascular mortality, in both treated patients (nadir 84, 80 mmHg respectively) and non-treated patients (nadir 90, 85 mmHg respectively) by Boutitie et al. [14]. For non-cardiovascular deaths, the relationship was J-shaped in the treated group (nadir 84 mmHg) and negative in the control group. Similar results were observed with SBP. These results suggest a complex relationship between risk reduction and treatment effect on blood pressure, and certainly not a linear one.

The HOT trial was designed to check that the lower the blood pressure on treatment, the lower the risk [25]. However, the results did not show any risk reduction in major cardiovascular events, the main outcome, between the extreme groups of target DBP, despite a blood pressure difference of 4 mmHg that should have been associated with a 30% relative reduction of stroke if the blood pressure difference explained all the risk reduction. The results from other trials as ALLHAT or STOP-2 that compared various antihypertensive drugs suggest that different treatments may achieve different risk reduction despite a similar effect on blood pressure [26,27]. The HOPE trial showed that in high-coronary risk participants, the angiotensin converting enzyme inhibitor ramipril compared with placebo decreased the occurrence of all cardiovascular outcomes significantly associated with high blood pressure, to an extent that could not be explained by the small average effect on blood pressure [28]. More recently the IDNT trial randomly compared placebo, amlodipine and irbesartan in old diabetic patients with overt nephropathy. There was a clear and significant difference in favour of the AII receptor blocker as compared with amlodipine on the primary combine endpoint and the risk of doubling the serum creatinine which was not explain by differences in blood pressure that were achieved [29].

However, in a comparison of various blood pressure-lowering regimens it was found that greater risk reduction was achieved with regimens that targeted lower blood pressure reduction [30]. Actually, this only means that there is a correlation between the extent to which the treatment lowers blood pressure and the risk reduction. That does not mean that all the risk reduction is explained by the treatment effect on blood pressure. More debating was the almost absence of differences in outcome among drug classes in this meta-analysis. This could be interpreted as evidence against our findings if the effect on blood pressure was exactly the same across all drugs, that we do not know.

Thus, several evidence coming up from a variety of trials are consistent with our findings. One can no longer accept the assumption that drugs given to hypertensive subjects act solely by decreasing blood pressure. There are other, yet unknown, probably drug-specific, mechanisms of action that explain the remaining effect. The apparent dissociation between coronary heart events and cerebrovascular events suggests the remaining part of the risk reduction not explained by the effect on blood pressure is because of specific treatment effect on alterations of the target organ hypertension-driven specific diseases.

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