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Editorial

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When should blood pressure be lowered? Should treatment be guided by blood pressure values or total cardiovascular risk?

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Recent hypertension guidelines [1-3], confronted with the question when to initiate antihypertensive treatment, have acknowledged that trial-based evidence about the blood pressure threshold deserving treatment is weak. Hence, their recommendations in favour or against intervention are necessarily based on experts' opinion or wisdom.

The issue about the poor level of the evidence favouring active blood pressure lowering in individuals with systolic and diastolic blood pressure (SBP/DBP) values within what is usually defined grade 1 hypertension (SBP 140-159 and/or DBP 90-99 mmHg) was first raised by my group in 2009 [4]: we called attention on the fact that the few trials performed in the 1970-80s on what was then defined as "mild" hypertension could not be taken as reliable evidence supporting treatment of grade 1 hypertension, as patients included in the mild hypertension trials had been recruited on the basis of DBP values only (often in a range much wider than the 90-99 mmHg range now used for grade 1 hypertension). Furthermore, in most of the trials SBP was not considered, and in some of them SBP could be as high as up to 200 mmHg.

In 2012 a Cochrane collaboration tried to overcome this difficulty by making an individual patient meta-analysis of the "mild" hypertension trials including only data from those patients whose blood pressure values were in the grade 1 range [5]. The meta-analysis was unable to show a significant reduction in the risk of any cardiovascular outcome, alone or in combination. These negative results were widely publicized as warning against overtreating grade 1 hypertension, though the number of patients and events that could be included was rather small (for example, the strokes considered were only 30), and the statistical power very low. A successive attempt by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) to accrue the number of patients and events (patients from 8912 to 15 239; major cardiovascular events from 161 to 662) by including other individuals from other trials with baseline SBP/DBP in the grade 1 range succeeded to show significant reductions in stroke, major cardiovascular events and mortality [6]. The BPLTTC conclusions, however, were limited by the fact that about 50% of the added individuals were already under some blood pressure lowering treatment at baseline and therefore could not be correctly defined as grade 1 hypertensive patients for whom a decision should be

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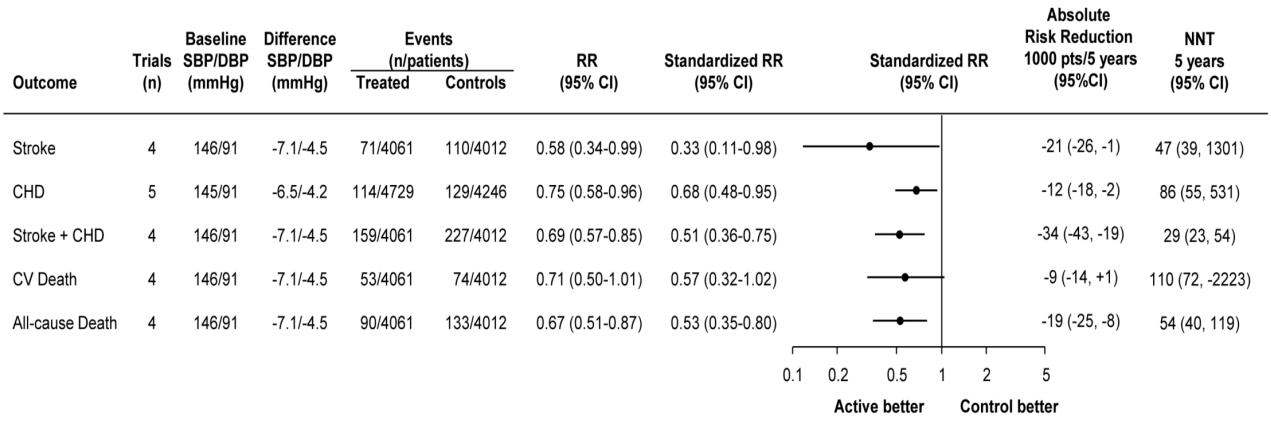

Figure 1. Effects of blood pressure lowering in trials with average baseline blood pressure in grade 1 and average low-moderate cardiovascular risk. Abbreviations: CHD, coronary heart disease; CI, confidence intervals; CV, cardiovascular; DBP, diastolic blood pressure; HT, hypertension; n, number; NNT, number needed to treat; pts, patients; RR, Mantel-Haenszel risk ratios; SBP, systolic blood pressure. Standardized RR is to a SBP/DBP reduction of 10/5 mmHg; The column Absolute Risk Reduction reports number (and 95% CI) of events prevented every 1000 patients treated for 5 years with a standardized RR. NNT are numbers (and 95% CI) of patients needed to treat for 5 years to prevent one event. CV death rate in the control group (index of CV risk) was 4.5% over 10 years. (From ref. 7, by courtesy of Journal of Hypertension).

taken about treatment initiation. Furthermore, most of the individuals added in the BPLTTC meta-analysis were diabetic and the meta-analysis results could not be extended to the general hypertensive population.

We have recently followed another meta-analytical approach. Among all the blood pressure lowering trials (active treatment vs placebo, or more active versus less active treatment) we have chosen all those in which patients were randomized in absence of current treatment, in order to avoid incorrectly labelling hypertension grade. We were able to identify 32 trials (including 104 359 patients) that could be classified as investigating grade 1, 2 or 3 hypertension on the basis of the average baseline blood pressure value in each trial [7]. Significant reductions of the risk of all major cardiovascular outcomes, considered in isolation or combined, were found to be induced by blood pressure lowering at all grades of hypertension with no trend toward different relative risk reductions at different hypertension grades. Support to the decision to provide blood pressure lowering treatment recommendations to patients with grade 1 hypertension, even when their total cardiovascular risk is low to moderate, was provided by a sensitivity meta-analysis, including only those grade 1 hypertension trials in which the groups randomized to placebo or less intense treatment had a cardiovascular death rate lower than 5% in 10 years. Figure 1 shows that in this analysis, including 8974 grade 1 hypertensives, 181 strokes, 243 coronary events and 223 deaths, blood pressure lowering treatment significantly reduced all major types of cardiovascular disease event and all-cause mortality: in these individuals with moderate blood pressure elevation and moderate total cardiovascular risk, not only relative cardiovascular risk reduction was substantial (49% reduction in major cardiovascular events), but also absolute risk reduction was important, amounting to 34 strokes and coronary events prevented every 1000 patients treated for 5 years.

The conclusions of our meta-analysis [7] have been further supported by the recently published results of the Heart Outcomes Prevention Evaluation (HOPE)-3 trial [8] which has shown a significant 27% reduction of major cardiovascular outcomes in patients at an intermediate level of cardiovascular risk with baseline SBP values higher than 143.5 mmHg (mean 154 mmHg), though no benefit of blood pressure lowering treatment was seen in individuals with lower baseline blood pressure values (high-normal blood pressure).

On the whole, despite the absence of a large randomized placebo-controlled trial specifically investigating blood pressure lowering treatment in patients with grade 1 hypertension at low to moderate cardiovascular risk, the data of our meta-analyses [7] and the results of the HOPE-3 subanalysis [8] provide a much stronger

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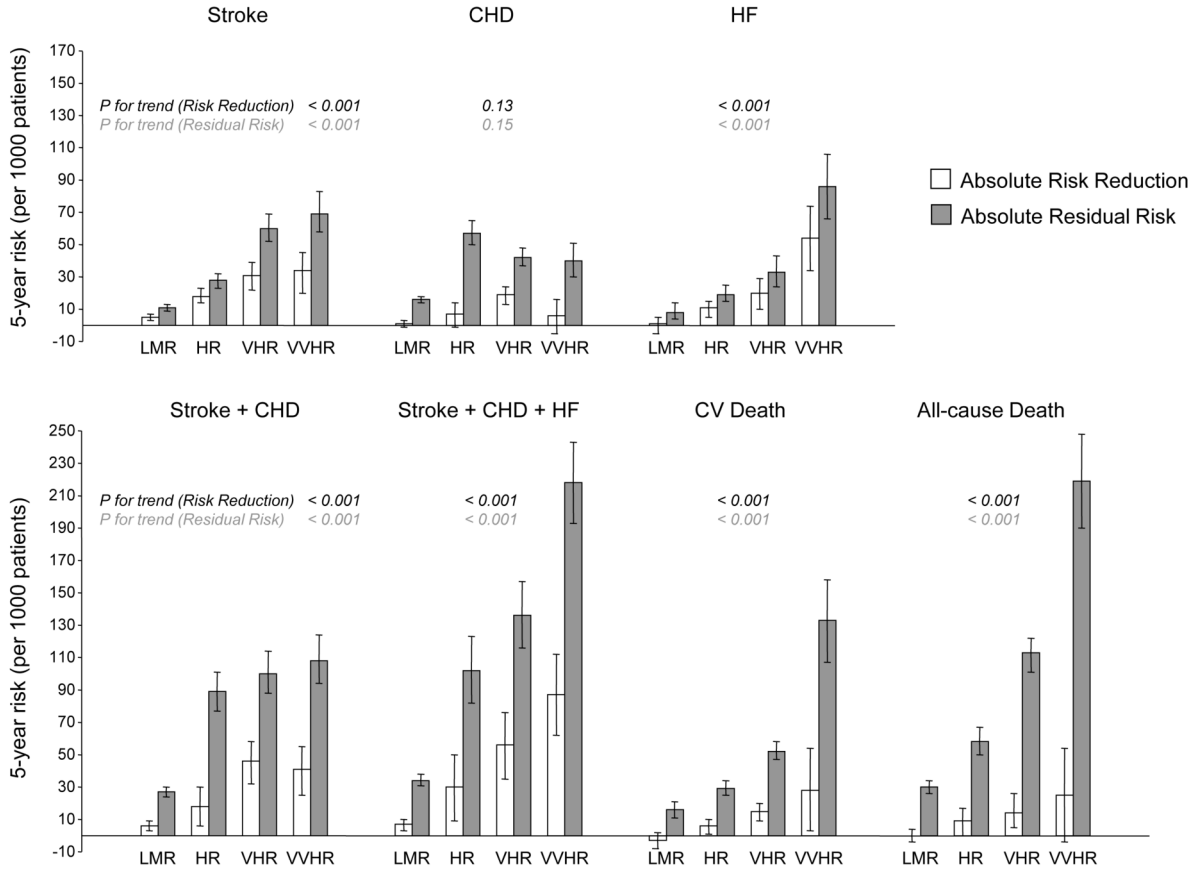

Figure 2. Absolute risk reduction by blood pressure lowering treatment (standardized to 10/5 mmHg SBP/DBP) and residual risk in trials stratified by increased level of cardiovascular risk in the control group. Abbreviations: CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; LMR, low-moderate risk; HR, high risk; VHR, very high risk; VVHR, very very high risk; y, years. Absolute risk reductions (empty rectangles) and residual risk (shaded rectangles) are expressed as number of events prevented or residual every 1000 patients treated for five years. Vertical bars are 95% confidence intervals. It is apparent that both benefits (risk reduction) and failures (residual risk) progressively increase with increasing level of risk, but residual risk, particularly of mortality, increases more markedly. (From ref. 12, by courtesy of Journal of Hypertension).

evidence-based support in favour of actively treating these individuals than the experts' opinion on which the recommendations of the 2013-2014 guidelines [1-3] were based [9, 10].

The blood pressure based approach to decide initiation of antihypertensive treatment, however, has been disputed by the opinion that a more beneficial, and cost-effective, approach should base treatment decisions on the level of existing total cardiovascular disease risk rather than blood pressure values. This position has been upheld by the Blood Pressure Lowering Treatment Trialists' Collaboration on the basis of an individual data meta-analysis of a 11 trials (51 917 patients) the data of which could be stratified according to individual cardiovascular risk level [11]. The finding that relative risk reduction of major cardiovascular events was similar at all levels of risk, and, consequently , absolute risk reduction significantly increased with the increase of total cardiovascular risk was interpreted by the authors as providing "support for the notion that blood pressure-lowering treatment should target those at greatest cardiovascular risk, not just those with the highest blood pressure levels" [11]. The authors' conclusion is that "a risk-based approach is likely to be more cost-effective than a blood pressure-based approach, and could simultaneously reduce the number of patients needing treatment, and control drug costs, while increasing the numbers of averted strokes and heart attacks" [11].

We have simultaneously conducted a similar meta-analysis with similar results, from which, however, we have drawn different conclusions [12]. We have subdi-

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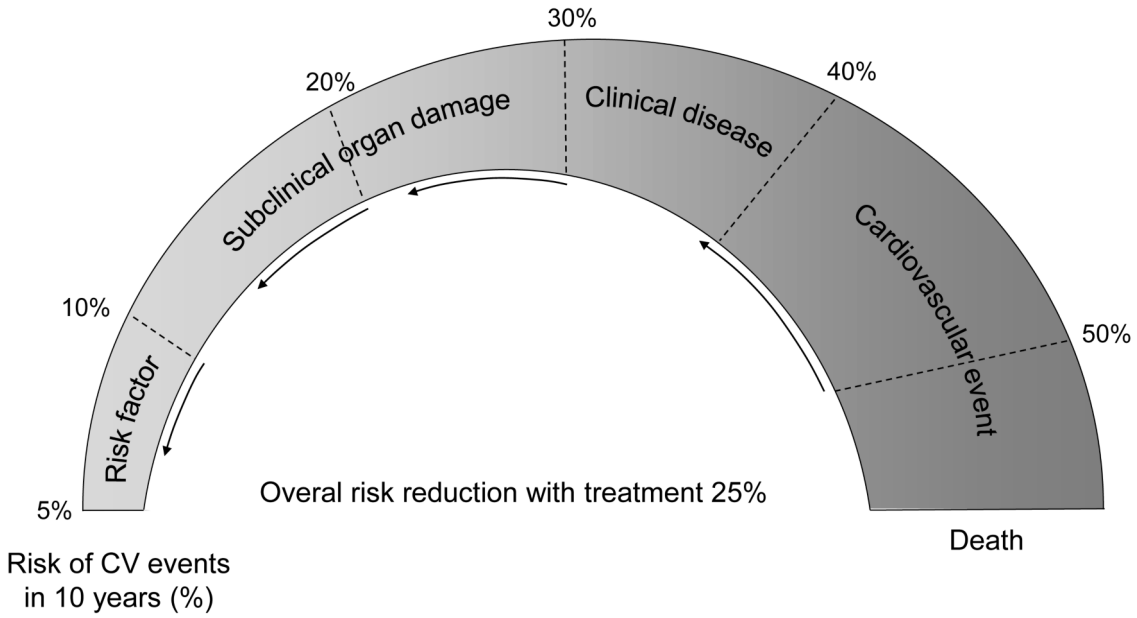

Figure 3. The natural history of cardiovascular disease. The CV continuum is a sequence of events beginning with risk factors such as hypertension and diabetes, leading to subclinical (asymptomatic) organ damage including left ventricular hypertrophy. If left untreated, this results in clinical (symptomatic) disease and ultimately cardiovascular events (stroke, myocardial infarction, heart failure) and death. Approximate risk is shown as % CV events expected in 10 years. The arrows indicate the residual level to which risk can be reduced depending on when treatment is initiated. Treatment benefit is calculated to be approximately 25% reduction of initial risk, as suggested by meta-analyses of trials. Abbreviation: CV, cardiovascular. (From ref. 13, by courtesy of Nature, Reviews of Cardiology).

vided the 68 blood pressure-lowering trials (245 885 patients) in four strata according to the level of total cardiovascular risk, measured as cardiovascular death incidence in the control group (placebo or less intense blood pressure lowering): less than 5% in 10 years, low-moderate risk; from 5% to less than 10% in 10 years, high risk; from 10% to less than 20% in 10 years, very high risk; 20% and above, very very high risk. We have also found that relative risk reduction of all outcomes did not differ between the various cardiovascular risk categories and, consequently, absolute risk reduction (the apparent benefits of treatment) significantly increased with increasing cardiovascular risk. However, Figure 2 shows that, with increasing cardiovascular risk, not only absolute risk reduction increased, but also absolute residual risk, that is the amount of cardiovascular events that could not be prevented by blood pressure lowering treatment, dramatically increased [12].

The suggestion to follow a risk based approach in deciding about initiation and intensity of antihypertensive treatment by "targeting" those at greatest cardiovascular risk, may appeal to health service managers with the promise of reducing monetary costs if treatment is delayed to a time when cardiovascular risk is high or very high. This money saving, however, means leaving the hypertensive patient at increased absolute "residual" risk of suffering an event even when treatment is initiated. Figure 3 illustrates the natural history of cardiovascular disease as a continuum of increasing risk [13]: at any stage of the continuum, blood pressure lowering is beneficial provided systolic or diastolic values are at least 140 or 90 mmHg, but absolute residual risk can be maintained low only if intervention is initiated before irreversible or scarcely reversible organ damage or cardiovascular disease develops.

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