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RESEARCH LETTER

Are we using blood pressure-lowering drugs appropriately? Perhaps now is the time for a change

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This topic seems particularly appropriate since this year is the 20th Anniversary of the Cochrane Collaboration. The Cochrane Collaboration and the Hypertension Review Group have played a leading role in advancing the evidence-based agenda that has challenged many of our ways of thinking and approaches to treating patients.

A BRIEF HISTORY OF STUDIED POPULATIONS FOR BP-LOWERING DRUG TREATMENT

Evidence on the benefits of blood pressure (BP)-lowering treatment fluctuates over time

The benefits of BP-lowering drugs have been tested in randomized controlled trials for more than 40 years. The first evidence came from moderate-to-severe hypertensive patients with diastolic BP above 100 mm Hg at the end of the 1960s.[1–3] However, the conclusion of the investigators regarding treatment efficiency did not meet current methodological standards. No formal statistical test was performed and if performed, it would have been inconclusive. Congestive heart failure was the only outcome that was significantly reduced and even this evidence required the increase in power through a meta-analytical approach conducted several decades later.[4] Furthermore, reducing congestive heart failure was not the primary objective of any of these trials. The Veterans Administration published results from the stratum of mild-to-moderate hypertension in 1970, but intention-to-treat results were not available, and 15% of the patients were lost to follow-up for mortality analysis (this point was confirmed after writing to the author).[5] During the late 1970s and early 1980s, four trials produced results on mild-to-moderate hypertension defined as diastolic BP between 90 and 110 mm Hg.[6–9] Only two[5,6] showed significant results on a predefined primary outcome combining largely cardiovascular complications of hypertension. In 1985, the MRC trial in 35- to 64-year olds[10] was the first one to definitely affirm the benefit from these drugs in hypertensive people with diastolic BP between 90 and 109 mm Hg. This benefit was mainly observed in terms of stroke, the primary outcome. During the same period, two trials assessed the benefits of BP-lowering drug treatment in hypertensive stroke survivors, without convincing results when observed alone, but showing a significant benefit on stroke recurrence when taken into account together.[4] This was confirmed later in a larger meta-analysis.[11] Of note, these early trials in stroke survivors recruited patients based both on systolic and diastolic BP, whereas among all the other trials previously cited diastolic BP elevation only was required, with the exception of the Oslo trial in which isolated systolic hypertension patients were also eligible. Between 1981 and 1992, the results from seven trials[12–18] in patients over 60 years of age were published, mixing inclusion criteria on systolic and diastolic BP, either high or normal for the latter, and always above 160 mm Hg for the former. These seven trials showed consistent results on stroke risk reduction, and their meta-analyses[19] showed a significant 10% risk reduction for overall mortality.

The last important piece of evidence concerned the benefit of BP-lowering drugs on cardiovascular risk even without hypertension. This has been shown by powerful trials such as HOPE[20] in high cardiovascular risk patients, and PROGRESS[21] in stroke survivors, with or without hypertension. Retrospectively, we can observe that this kind of evidence was already present, with the clear benefits observed from beta-blockers and angiotensin converting enzyme inhibitors after myocardial infarction, and in patients with congestive heart failure. Of note in this context, the role of BP lowering in risk reduction has only rarely been offered as an explanation for the effect.

Background of the guidelines evolution regarding BP thresholds

The guidelines for BP-lowering drug use followed the development of this knowledge, but with some liberty regarding the definition of hypertension. The initial stress on diastolic BP was enlarged to take systolic into account, necessary to define indications in older hypertensive individuals, in whom low diastolic BP is not only frequent, but also an aggravating risk factor. The reversal of the association between diastolic BP and risk occurs around 60 years of age.[22] The difficulty in translating the complex association between systolic and diastolic BP, age and cardiovascular risk into simple practical rules, is further amplified by the lack of a natural threshold to define hypertension: above 120 mm Hg of systolic BP, all strata display a risk higher than the nearest lower one.[23] As a consequence, this continuous relationship makes all attempts to define hypertension arbitrary. This explains why these thresholds are often called into question, and the cardiovascular risk level approach is often proposed to replace or at least complement them in guidelines.[24]

This rapid overview shows that an appropriate level of evidence is only available for hypertensive patients over 60 years of age with a systolic BP of 160 mm Hg and above. There did not seem to be a convincing answer to the question of the benefit-to-risk ratio in mild hypertension, defined by a diastolic BP between 90 and 99 mm Hg, and/or a systolic BP between 140 and 159 mm Hg. Answering this question was the objective of a systematic review published in the Cochrane Library in August 2012.

AN INCREDIBLE LACK OF EVIDENCE FOR BENEFITS ON MILD HYPERTENSION

Reminder of the principal results

When looking at all the available evidence, only four trials provided specific data on the primary prevention of mild hypertension, with a total of 8912 participants for total mortality, and 7080 participants for non-fatal and fatal outcomes. None of the outcomes demonstrated a significant benefit of drug therapy compared with placebo: relative risk for total mortality was 0.85 (95% CI: 0.63, 1.15), for coronary heart disease 1.12 (95% CI: 0.80, 1.57), for stroke 0.51 (95% CI: 0.24, 1.08) and for total cardiovascular events 0.97 (95% CI: 0.72, 1.32). Based on the largest trial, the rate of withdrawals because of adverse effects was increased by more than fourfold in the drug therapy group

compared with the control (RR: 4.80, 95% CI: 4.14, 5.57); in absolute terms, this means that approximately one patient in ten receiving antihypertensive therapy had an adverse event leading to withdrawal.

Half of the hypertensive population

Lowering the threshold definition of hypertension was not examined in the light of its economic aspects. The distribution of risk factors coupled with the age and sex structure of the real French population allowed us to generate a virtual population, with which it was possible to compute that primary prevention mild hypertensive patients make up more than half of the total population of hypertensive patients.[25] This estimate may not be accurate for other populations, but it provides a sense of the order of magnitude of the importance of the group with mild hypertension. Summing up the information from randomized controlled trials in all categories of hypertension gives a statistically significant benefit for all outcomes. Subgroup analyses raise the issue of increasing risks, and both false positives and false negatives. However, the size of this sub-group, representing more than half the eligible population for treatment, is a strong rationale to focus on this principal subgroup.

Treating low-risk people could be a high-risk strategy

The most logical way to extrapolate results from clinical trials is using the effect-model law,[26] which describes the risk expected under treatment as a function of the risk without treatment. In cardiovascular prevention, this function is frequently assumed to be a mere multiplication, by a coefficient estimated as the relative risk from a meta-analysis. The absolute benefit is directly proportional to the spontaneous risk, which justifies prioritizing treatment of high-risk people.

For other similar risk factors, mild hypertensive individuals have a lower risk than those with moderate or severe hypertension. They also have a lower expected absolute benefit, which could be more easily counterbalanced with side effects of the treatment, potentially leading to an unfavorable benefit-to-harm balance.

HOW TO DEAL WITH THIS INFORMATION? LET US INFORM PATIENTS!

Editors' and experts' positions about how to deal with such inconclusive results in practice are divergent.[27–29] The minimum on which all experts must agree is that the physician in charge, must tell the truth to his/her patients regarding the benefit from treatment they are proposing. In this case, they must say that he/she does not know whether the benefit-to-harm balance is favorable or unfavorable.

In parallel to that information, physicians have to explain that the definitions of hypertension have always been arbitrary, subject to change and do not define high-risk situations by themselves, or situations that are consistently associated with benefit from treatment.

IMPLICATIONS FOR RESEARCH

Some BP-lowering drugs such as β-blockers and ACE inhibitors have been assessed in cardiovascular prevention in high-risk groups, after coronary events, in congestive heart failure, or in patients selected based on the association of several risk factors. In these settings, they have been regularly associated with significant benefit on cardiovascular outcome fatal or not, even in sub-groups of patients without hypertension. The precise role of BP lowering in this risk reduction is a matter of debate. That such drugs could be associated with some benefit in low-risk hypertensive people is possible but not demonstrated today, and is challenged by the low expected absolute benefit. Progress for managing risk in this population is expected from (1) a better understanding of the relationship between individual characteristics and the benefit and side effects of treatment; (2) the availability of tools to display on the physician's desk computer the information on the benefits and the risks from treatment options adjusted to a given patient's profile; (3) increasing the level of evidence regarding the benefit-to-harm ratio of BP-lowering drugs in primary prevention mild-hypertension patients. The latter would require conducting a specific clinical trial. One may be tempted to design a treatment withdrawal trial, which could be very useful if it would demonstrate that withdrawal is possible without trouble. However, if such a trial showed a benefit in continuing treatment that would not be equivalent to the required prospective randomized clinical trial. Conducting such a trial is definitely not unethical. Treating millions of patients without knowing whether benefits outweigh harms is obviously far from ethical and is not common sense.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 Wolff FW, Lindeman RD. Effects of treatment in hypertension: results of a controlled study. *J Chron Dis* 1966; **19**: 227–240.
2 Veterans Administration Cooperative Study Group on antihypertensive agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA* 1967; **202**: 1028–1034.
3 Barraclough M, Weddel JM. Control of moderately raised blood pressure: report of a co-operative randomised controlled trial. *BMJ* 1973; **3**: 434–436.
4 Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment trials of hypertension: improving the estimate of therapeutic benefit. *J Hum Hypertension* 1996; **10**: 1–8.
5 Veterans Administration Cooperative Study Group on antihypertensive agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 1970; **213**: 1143–1152.
6 McFate Smith W. for the US Public Health Service Hospitals Co-operative Study Group. Treatment of mild hypertension: results of a ten year intervention trial. *Circ Res* 1977; **40**(suppl I): 98–105.
7 Evaluation of drug treatment in mild hypertension: VA - NHLBI feasibility trial. *Ann NY Acad Sci* 1978; **304**: 267–288.
8 Helgeland A. Treatment of mild hypertension: a five year controlled drug trial: the Oslo Study. *Am J Med* 1980; **69**: 725–732.
9 Management Committee. The Australian therapeutic trial in mild hypertension. *Lancet* 1980; **i**: 1261–1267.
10 Medical Research Council Working Party. MRC Trial of treatment of mild hypertension: principal results. *BMJ* 1985; **291**: 97–104.
11 The INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) Project CollaboratorsGueyffier F, Boissel J-P, Boutitie F, Pocock S, Coope J, Cutler J

et al. The effect of antihypertensive treatment in patients having already suffered from stroke. Gathering the evidence. *Stroke* 1997; **28**: 2557–2562.
12 Sprackling ME, Mitchell JRA, Short AH, Watt G. Blood pressure reduction in the elderly: a randomised controlled trial of methyldopa. *BMJ* 1981; **283**: 1151–1153.
13 Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *BMJ* 1986; **293**: 1145–1151.
14 Amery A, Birkenhäger W, Brixko P, Bulpitt C, Clement D, de Leeuw P *et al*. Influence of antihypertensive drug treatment on morbidity and mortality in patients over the age of 60 years. EWPHE results: sub-group analysis based on entry stratification. *J Hypertens* 1986; **4**: S642–S647.
15 Perry HM Jr, Smith WM, McDonald RH, Black D, Cutler JA, Furberg CD *et al*. Morbidity and mortality in the Systolic Hypertension in the Elderly Program Pilot Study. *Stroke* 1989; **20**: 4–13.
16 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**: 3255–3264.
17 Dalhöf B, Lindholm L, Hansson L, Scherstén B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP - Hypertension). *Lancet* 1991; **338**: 1281–1285.
18 Medical Research Council Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992; **304**: 405–412.
19 Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev* 2009; **4**: Art. No. CD000028.
20 HOPE (Heart Outcomes Prevention Evaluation) Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**: 145–153.
21 PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; **358**: 1033–1041.
22 Staessen JA, Gasowski J, Thijs L, Den Hond ED, Boissel JP, Coope J *et al*. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000; **355**: 865–872.
23 Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data from one million adults in 61prospective studies. *Lancet* 2002; **360**: 1903–1913.
24 McMahon S, Neal B, Rodgers A. Hypertension—time to move on. *Lancet* 2005; **365**: 1108–1109.
25 Marchant I, Nony P, Cucherat M, Boissel JP, Thomas SR, Bejan-Angoulvant T *et al*. The global risk approach should be better applied in french hypertensive patients: a comparison between simulation and observation studies. *PLoS One* 2011; **6**: e17508.
26 Boissel JP, Kahoul R, Amsallem E, Gueyffier F, Haugh M, Boissel FH. Towards personalized medicine: exploring the consequences of the effect model-based approach. *Per Med* 2011; **8**: 581–586.
27 Godlee F. Overtreatment, over here. *BMJ* 2012; **345**: e6684.
28 Mitka M. Clinicians remain reluctant to allow negative findings to influence practice. *JAMA* 2012; **308**: 1305–1306.
29 Brophy J. ACP Journal Club. Review: low-quality evidence fails to show that antihypertensive drugs affect outcomes in mild hypertension. *Ann Intern Med* 2012; **157**: JC6–JC6.