Hypertension guidelines, meta-analyses and clinical trials: do we assume too much?

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ABSTRACT

- Given fundamental differences in the recommendations in guidelines from major national and international committees, we cannot rely on them unquestioningly.
- Different antihypertensive agents are known to have differing effects according to age and race.
- Exchanging (rather than following guideline recommendations of adding to) an ineffective first-line antihypertensive drug can result in control of hypertension with monotherapy.
- Conclusions about a preferable first-line antihypertensive agent are limited by trial protocols with varying drug doses and questionable drug combinations.
- Guidelines are often based on meta-analyses of drugs of a particular class, which could ignore important differences between drugs within a class.
- Trials of 3–5 years cannot determine the long-term effects of drugs which patients often take for decades.

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We live in an era of evidence-based medicine, in which clinical guidelines from authoritative bodies are available in all specialties. A question not often asked, but relevant to hypertension in 2005, is whether we can always rely on guidelines.

Four authoritative guidelines on managing hypertension were released in 2003.[1-4] While there was substantial agreement between them, a new recommendation in the 7th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) guidelines — that thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension[1] — was not shared with the other guidelines.[2-4]

The preference for thiazides in JNC7 was motivated largely by the publication of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[5] and a subsequent meta-analysis that was substantially influenced by inclusion of the ALLHAT data.[6] ALLHAT was designed to answer the question of whether the newer classes of antihypertensive drugs are as good as or better than diuretics in reducing myocardial infarction and coronary disease (CHD) mortality.[5] Nearly 45 000 patients with hypertension and one additional risk factor for CHD were randomly allocated to initial therapy with chlorthalidone (a thiazide diuretic), amlodipine (a calcium-channel blocker), lisinopril (an angiotensin-converting enzyme inhibitor) or doxazosin (an α-blocker). An interim analysis found an increased incidence of heart failure with doxazosin and the doxazosin arm was prematurely terminated. At the end of the study there was no difference in the primary endpoint of combined fatal CHD or non-fatal myocardial infarction between the chlorthalidone, amlodipine and lisinopril arms, but, compared with chlorthalidone, a higher rate of heart failure was seen with amlodipine and a higher incidence of stroke and heart failure was observed with lisinopril. The ALLHAT investigators concluded that thiazide diuretics are superior in preventing one or more major forms of cardiovascular disease.

These conclusions have since been widely questioned,[2,7-10] and I argue that this questioning should be extended beyond ALLHAT to encompass the assumptions that underlie the comparison of antihypertensive drugs in all the trials and meta-analyses.

Assumptions of comparative drug studies and meta-analyses in hypertension

Placebo-controlled trials of a number of different antihypertensive drugs have shown the beneficial effect of lowering blood pressure.[11] More recently, a number of large clinical trials have compared the effects of different antihypertensive drugs,[5,12-20] but it needs to be considered that these trials, even when combined in a meta-analysis,[6,11] may not have the ability to detect clinically important differences between drugs.

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All hypertension is the same

Large hypertension studies include a wide spectrum of patients with elevated blood pressure, assuming that these patients have the same condition. However, there is evidence to suggest that all hypertension is not the same. For example, there are recognised differences in blood pressure responses to antihypertensive medication depending on age and race. Hypertension in young (< 60 years) white patients tends to respond best to angiotensin-converting enzyme (ACE) inhibitors and β-blockers, and least well to diuretics.[21] Hypertension in older white patients responds best to diuretics and calcium-channel blockers (CCB),[21] whereas hypertension in black patients of all ages is poorly responsive to ACE inhibitors.[21] These effects of age and race are at least partly related to baseline plasma renin activity, with low renin activity predicting a response to diuretics and high renin activity predicting a response to ACE inhibitors.[22]

These differences in the pathophysiology of hypertension have particular implications for the interpretation of ALLHAT and JNC7. ALLHAT included 32% black Americans, a subgroup in whom a greater blood pressure response was both expected and observed with chlorthalidone compared with lisinopril.[5] Even performing such a comparison in black Americans can be questioned, as it ignores the simple common sense of first using the drug most likely to control their blood pressure. Furthermore, with the evidence that diuretics are the least effective agent in

patients under the age of 60 years,[21] in conjunction with the knowledge that ALLHAT only included patients aged 55 years or older,[5] the recommendation of JNC7 for preferential use of thiazides in patients of all ages seems hard to justify.

Stepped care is better than sequential therapy

In the absence of adequate blood pressure control with monotherapy, most comparative drug trials have added drugs (stepped design) rather than exchanged them (sequential design). However, no large trial has compared the effectiveness of these two regimens. Furthermore, there is evidence that, in a significant proportion of patients, mild to moderate hypertension can be controlled by monotherapy if managed with a sequential regimen.[23,24] In young patients with hypertension in whom initial monotherapy has failed, the best swap was found to be from a renin-inhibiting agent (ACE inhibitor or β-blocker) to a "volume reducing agent" (diuretic or CCB), or vice versa.[23] When possible, monotherapy would seem preferable for reasons of simplicity, compliance and expense, yet the need for multiple agents with stepped therapy will be self-fulfilling in all patients who do not, or who only partially, respond to a first-line agent.

Drugs added in the 2nd and 3rd steps of a stepped-care approach are not important

A fundamental assumption of ALLHAT[5] and a recent meta-analysis of antihypertensive trials[6] is that only the first-line agent of a stepped regimen is responsible for the effects. Interpretation on this basis clearly has limitations when more than 60% of the patients are treated with two or three antihypertensive drugs.[5] Furthermore, there is evidence that some combinations of drugs are better than others.[25] Indeed, not only was the design of ALLHAT criticised because the choice of second-line and third-line drugs was not rationally based,[9] but this criticism is supported by the differences in blood pressure control achieved with the different drug regimens.[5]

Any important differences in drug efficacy will be apparent during 3–5 years

Antihypertensive treatment will be required for decades in many patients with hypertension. However, there are no long-term comparative drug trials in hypertension because of practical issues such as cost. No discernible difference between two antihypertensive agents at 3–5 years does not exclude clinically important long-term differences between the agents. Importantly, previous evidence that thiazides are associated with an increased risk of diabetes was confirmed by ALLHAT,[5] whereas there is accumulating evidence that inhibiting the renin–angiotensin system results in less diabetes.[16,26] The potential for adverse cardiovascular outcomes due to new cases of diabetes arising because thiazide diuretics are used in preference to ACE inhibitors is cause for concern,[27] and cannot be excluded by trials with follow-up of less than 5 years.

Drug doses are not important in their effects on endpoints

Most drug studies include a titration phase which allows for variable doses of the medication being used in a study, depending on blood pressure effects. However, the dose of a drug may be important for a particular mechanism, and variations in metabolism of and response to drugs could influence the effects of a drug in an individual.[28] The evidence for ACE inhibitors preventing cardiovascular events comes from randomised, placebo-controlled trials using the large doses of either 10 mg/day of ramipril[26] or 8 mg/day of perindopril,[29] and similar efficacy for lower doses of these agents cannot be assumed. However, the comparative studies and meta-analyses have not taken drug doses into consideration.

All antihypertensive drugs in the same class are the same

In the meta-analyses, drugs of the same class are combined,[6,11] but there are not only many known differences in the pharmacological properties of drugs in the same class,[28] there may also be important unrecognised differences. A genuine effect of a particular drug could be missed in a meta-analysis if other drugs in the same class did not share the effect.

Summary and implications

First, if there can be fundamental differences in the recommendations in guidelines, we cannot rely on them unquestioningly just because they come from major national or international committees. Second, there are a number of assumptions which underlie the comparative drug trials and meta-analyses in hypertension and which need to be understood before using their findings to guide the choice of the initial antihypertensive drug for individual patients. In contrast to recent recommendations for the preferential use of diuretics,[1] there is uncertainty about whether there is (or can be) a best initial drug for all hypertension. Doctors treat individuals, not populations, and the benefits of a particular antihypertensive drug are not likely to be equal for different patients. For example, there is evidence that thiazides are not an appropriate first choice in young patients and are relatively contraindicated in patients at significant risk of developing diabetes. Third, we can best manage individual patients with hypertension when we take into account all their clinical conditions; understand the pathophysiology of hypertension and the mechanisms by which antihypertensive agents act; understand the methods, results and limitations of the major clinical studies; and combine this information in our decision making. Unfortunately, this combination is a tall order, as a detailed knowledge of the major clinical studies is just not practicable for most practitioners, many of whom will not even read the relevant guidelines. Last, we need further antihypertensive drug trials in specific populations. Assessment of blood pressure control in new trials will need to include 24-hour ambulatory or home blood pressure monitoring in view of increasing evidence of the value of these techniques.[30]

Competing interests

None identified.

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