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REVIEW ARTICLE

Should we prefer different drugs to treat hypertension in older and younger adults?

Practical implications of clinical trials: American perspective

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KEY WORDS

aging, antihypertensive agents, blood pressure, cardiovascular risk, hypertension

ABSTRACT

Whether older and younger persons derive similar benefit from antihypertensive treatment and whether treatment choices should be tailored to the age of the patient are unresolved issues about which there is a paucity of evidence. The Blood Pressure Lowering Treatment Trialists' Collaboration has attempted to address this deficiency in a meta-analysis that included 31 trials with 190,606 participants. They compared the proportionate risk reductions achieved with different classes of antihypertensive drugs in younger (<65 years) and older (>65 years) adults. They reported that there was no clear evidence to support recommendations for particular antihypertensive drug classes in older or younger adults. In this paper we discussed the Trialists' paper and its limitations and strenghts, current guidelines recommendations, and the major conclusions that are important for clinicians.

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The Blood Pressure Lowering Treatment Trialists' (BPLTTC) analysis of outcomes of antihypertensive treatment in older and younger adults Whether older and younger persons derive similar benefit from antihypertensive treatment and whether treatment choices should be tailored to the age of the patient are unresolved issues about which there is a paucity of evidence. The BPLTTC has attempted to address this deficiency by comparing the relative reductions in blood pressure (BP) and cardiovascular disease risk achieved with different BP lowering regimens in younger and older adults.[1] The Trialists compared the proportionate risk reductions achieved with different classes of antihypertensive drugs in younger (<65 years) and older (≥65 years) adults enrolled in randomized controlled trials in a meta-analysis that included 31 trials with 190,606 participants. The treatment regimens that were compared were those previously reported in the Trialists' second main cycle of overviews: angiotensin-converting enzyme inhibitors (ACEI) vs. placebo, calcium channel blocker (CCB) vs. placebo, more intensive vs. less intensive BP lowering regimens, angiotensin receptor blockers (ARB) vs. control regimen, ACEI vs. diuretics/β-blockers (BB), CCB vs. diuretics/BBs, and ACEI vs. CCBs.[2] Additional comparisons, particularly relevant to some current treatment guidelines, included ACEI or CCB vs. BBs and ACEI or CCB vs. diuretics in the older and younger age groups. The age cut-offs specified above were chosen because most participating trials used the same categories in their own subgroup analyses.

There was no significant difference between age groups in the effects of lowering BP and no age-dependent difference between the effects of the drug classes on major cardiovascular events. Further, there was no significant interaction between age and the effects of treatment when age was fitted as a continuous variable and overall effects were estimated across trials. Meta-regression analysis of the effects of BP lowering in the 2 age groups also showed no difference between groups in the risk reduction achieved/unit reduction in BP for the primary outcome of major cardiovascular events or for any secondary outcome.

The Trialists concluded that BP reduction produces benefit in both younger (<65 years) and

older (>65 years) adults, with no strong evidence that protection against major vascular events afforded by different drug classes varies substantially with age. Thus, they reported that there was no clear evidence to support recommendations for particular antihypertensive drug classes in older or younger adults, as included in some current treatment guidelines.[3-5]

British and Canadian guidelines recommend modifying antihypertensive treatment according to patient's age The Trialists' analysis does not support the recommendations of the British Joint Societies' guidelines on prevention of cardiovascular disease that hypertensive patients aged ≥55 should start treatment with either a CCB or a thiazide-type diuretic and that an ACEI or ARB is preferred in those <55 years of age.[3,4] These recommendations are based on evidence from renin-profiling studies that younger people (<55 years) and Caucasians tend to have higher renin levels than older people (≥55 years) and Blacks of any age.[6-8] Therefore, the guideline writers concluded that renin-angiotensin-aldosterone system (RAAS) blockade with ACEI, or ARB treatment would be more effective as initial BP lowering therapy for younger Caucasian patients than for older Caucasian or Black patients of any age, as these drugs decrease BP in part by suppressing the RAAS.

This line of reasoning suggests that older patients and Black patients of any age, who tend to be volume expanded and to have low renin levels, should be more responsive to other antihypertensive drug classes, i.e. diuretics and CCBs. In part, these conclusions are supported by clinical trial data. For example, 3 cooperative studies by the Department of Veterans Affairs in the USA showed that thiazide diuretics were more effective in older patients than in younger ones and, in particular, had a greater effect on systolic BP in older patients.[9] The Department of Veterans Affairs Single-drug Therapy of Hypertension Study, which compared the BP effects of representatives of 6 antihypertensive drug classes to placebo, showed that among male veterans, age and race had an important effect on the response to single-drug therapy for hypertension.[10] CCB treatment lowered BP more effectively than other drug classes in older veterans, particularly in Blacks, while ACEI treatment was most effective and diuretic treatment least effective in younger Caucasians. Interestingly, age and race were more robust predictors of therapeutic response than baseline renin profile in this study.[11] In contrast, the Treatment of Mild Hypertension Study (TOMHS), which compared the BP lowering effects of low doses of representatives of 5 leading antihypertensive drug classes to placebo, found no differences between active treatments.[12] This is likely due to the homogeneous study population of TOMHS, which included only younger, mainly Caucasian patients with stage 1 hypertension. Of note, none of these studies had cardiovascular disease and mortality outcomes.

Unlike most older guidelines, the British and Canadian guidelines do not recommend use of BBs as initial therapy for hypertension except in special cases, e.g. in younger people, those with increased sympathetic drive or intolerance to ACEI or ARB, and women of childbearing potential.[3-5] The recommendation that BBs not be used as first line treatment in older patients was based on evidence from randomized controlled trials that traditional BBs, particularly atenolol, are ineffective in lowering BP and preventing cardiovascular disease outcomes in this age group.[13-17] The British guidelines recommend that BBs generally be reserved as 4th line therapy for older patients who fail to achieve BP control on a triple combination of ACEI/ARB + CCB + thiazide-type diuretic and for those with a "compelling indication" for BB use, e.g. coronary artery disease. The rationale for choosing BBs for younger hypertensive patients includes the observation that younger persons in the early stages of hypertension frequently have a hyperdynamic circulation associated with increased sympathetic nervous system activity, as well as RAAS activation.[18] Sympatholytic interventions, including BB therapy, would be expected to be effective in lowering BP in such individuals.

USA and European guidelines do not recommend stratifying antihypertensive treatment by patient's age Unlike the British and Canadian guidelines, and consistent with the Trialists' meta-analysis, the Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high BP and the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) do not recommend that antihypertensive treatment choices be based on the patient's age.[19,20] The ESH/ESC guidelines support the concepts that the main benefits of antihypertensive treatment are due to BP lowering *per se* and are largely independent of the drugs employed and that all classes of antihypertensive drugs that have been shown to effectively lower BP and reduce cardiovascular outcomes, i.e. thiazide and thiazide-like diuretics, BBs, CCBs, ACEI and ARB, are suitable for the initiation and maintenance of antihypertensive therapy. While these guidelines acknowledge that individual patient characteristics, e.g. the presence of subclinical target organ damage, underlying cardiovascular disease or other important comorbidities, may dictate specific treatment choices, they do not identify age as such a determinant.

Antihypertensive treatment in the younger patient… What clinical trials don't tell us Age is, however, an important consideration when calculating the benefit and cost-effectiveness of antihypertensive treatment. In younger, low-risk

hypertensive patients, the benefit of treatment appears small when calculated over a treatment period of 5 years, as in most randomized controlled outcome trials. Therefore, these trials exclude younger patients. The short term goal in these patients is not to prevent a morbid or mortal cardiovascular event, which is unlikely, but to prevent the acceleration of hypertension and the onset and/or progression of subclinical target organ damage that will eventually result in overt cardiovascular disease and death.[21,22] Thus, while early institution of antihypertensive treatment in younger individuals may be highly beneficial, the benefit is deferred and is difficult to assess by usual methods. As pointed out by Zanchetti, in younger hypertensive persons, actuarial data from life insurance companies or other sources may provide a better assessment of treatment benefit than trial data.[22] In addition, development of more rigorous and validated methods of assessing the prognostic significance of biomarkers and subclinical target organ damage may be helpful in this regard.

Limitations of the Trialists' meta analysis The Trialists's meta-analysis suffers from the limitations of its component studies, including the failure to provide information about treatment effects in younger hypertensive patients. Most of the trials included in the analysis excluded participants <55 years in order to assure sufficiently high event rates with reasonable sample sizes. Thus, the mean age of participants in the younger and older groups was 57 and 72 years, respectively, and the 15 year age difference between the groups may not have been large enough to detect a real difference in the effectiveness of BP lowering between age groups. Similarly, because most patients in the trials fell within a fairly limited age range, the analysis was not informative regarding the outcome effects of antihypertensive treatment in the very elderly.

The benefits of reducing BP in very elderly patients have been established by the positive findings of the recently published HYpertension in the Very Elderly Trial (HYVET).[23] HYVET enrolled 3845 hypertensives, aged ≥80 years, with a baseline systolic BP >160 mmHg and no dementia or serious illness and randomized them to either active treatment with indapamide ±the ACEI perindopril or placebo. Active treatment resulted in a mean BP reduction of 15/6 mmHg and statistically significant reductions in total mortality (–21%), fatal stroke (–39%), heart failure (–64%) and the combined endpoint of cardiovascular events (–34%) compared to placebo after 2 years. Benefit was seen early and the treatment was well tolerated. The authors caution that these results cannot be extrapolated to the entire elderly population, as patients with dementia and frailty were excluded. Further, the treatment goal was a systolic BP of 150 mmHg, and results of the trial do not allow us to weigh the risks and benefits of lowering BP to more aggressive goals in this patient population.

Additional limitations of the Trialists' meta-analysis may have blunted their ability to detect real differences in treatment effects between age groups. These include differences in baseline BP, gender distribution and comorbidities between age groups; the short duration of follow-up in most trials, which makes it impossible to evaluate possible longer-term differential effects of treatment, and incomplete adherence to randomized treatments and extensive use of add-on therapies. Use of a composite outcome of major cardiovascular events as the basis for primary analyses is also problematic in that the type of cardiovascular event varies between age groups, stroke (which is more strongly affected by BP lowering) being more common in the older age group. This would tend to inflate the magnitude of the proportional reduction in events seen in the older compared to the younger group.

SUMMARY Despite these limitations, the very large number of patients included in the analyses, the care with which the data were collected and analyzed and the consistency of results obtained using different statistical techniques provide reassurance that the findings of the Trialists' analysis are real. The major conclusions that are important for clinicians are:

1) BP reduction produces similar proportional reductions in risks of vascular events in younger (<65 years) and older (≥65 years) adults, with the caveat that there is a paucity of data for those <50 years
2) absolute benefits of treatment are likely larger among older individuals because of their high absolute risk
3) there is no clear evidence to support recommendations for particular drug classes in older vs. younger adults.

The final conclusion should perhaps be tempered by the caveat that outcome data are very limited for younger (<50 years) hypertensive patients, and use of surrogate outcomes, including BP reduction, in making clinical decisions is controversial. Further, the question of which antihypertensive drug class is preferred for initial treatment of hypertension in either age group has diminished in importance as we have learned that most patients will require a combination of at least two drugs to achieve the accepted BP goals. For example, in the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT), 62.5% of patients needed ≥2 drugs after 5 years of follow-up to reach a goal of <140/90 mmHg.[24,25]

The question of which combinations are better is beginning to be asked in randomized controlled trials. The first major trial to test the outcomes of starting with combination therapy, the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with

Systolic Hypertension (ACCOMPLISH) trial, found very high (nearly 80%) BP control rates in both treatment arms.[26-28] Preliminary results of ACCOMPLISH have revealed a major 20% reduction in cardiovascular events with a CCB–ACEI combination compared to a diuretic–ACEI combination in the absence of major BP differences between arms. Further study is needed to identify which drug combinations are most effective and safest in different patient groups, including older and younger persons. It is important to remember that safety can become an overriding consideration in some patients, e.g. women of childbearoing potential, in whom RAAS blockers are contraindicated because of the risk of fetal developmental abnormalities.

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