

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

Practical implications of clinical trials: European perspective

Paolo Verdecchia¹, Giorgio Gentile², Fabio Angeli¹, Gianpaolo Reboldi²

¹ Department of Cardiology, Clinical Research Unit "Preventive Cardiology" Hospital "Santa Maria della Misericordia", Perugia, Italy

² Department of Internal Medicine, University of Perugia, Italy

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ABSTRACT

Guidelines for the management of hypertension almost invariably include sections where the evidence for or against treatment or for certain types of treatment in certain types of patients is inconclusive. This is especially the case of older patients with hypertension. As a consequence, although a large number of randomized trials including hypertensive patients aged ≥ 60 years showed that antihypertensive drugs reduce cardiovascular morbidity and mortality, health care professionals who take care of older adults have been often reluctant to provide adequate antihypertensive therapy. In a recent meta-analysis, the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) compared the effects of different drugs for reducing blood pressure (BP) in older and younger adults; the reduction in BP levels and the relative risk reduction of a cardiovascular event with various antihypertensive drugs occurred independently of the patients' ages, and the benefits of antihypertensive regimens based on different drug classes were widely comparable across age groups. The BPLTTC analysis strongly suggests an early and aggressive management of hypertension irrespectively of age; more myocardial infarctions, strokes, heart failures and deaths will be prevented by treating hypertensive patients aged ≥ 65 years than by treating patients ≤ 50 years with the same BP levels. Antihypertensive treatment should be embedded within the management of global cardiovascular risk, with the use of charts for stratifying risk based on additional risk factors, target organ damage or additional clinical conditions.

Guidelines for the management of hypertension almost invariably include sections where the evidence for or against treatment or for certain types of treatment in certain types of patients is inconclusive. This is especially the case of older patients with hypertension.^{1,2}

Epidemiologic studies showed that the positive relationship between elevated blood pressure (BP) levels and excess mortality between the ages of 60 and 69 years became an inverse relationship in men older than 75 years and in women older than 85, with older patients with higher BP living longer.³ Additionally, a trend analysis suggested that antihypertensive drugs might be less effective or even harmful in very old (> 80 years) hypertensive patients^{4,5}, and similar

concerns were raised by a later meta-analysis⁶. Finally, Hypertension in the Very Elderly Trial (HYVET-Pilot) data indicated that antihypertensive drugs in the very old were associated with a reduction of stroke events, but not of total mortality.⁷ As a consequence, although a large number of randomized trials including patients aged ≥ 60 years affected by systolic-diastolic hypertension or isolated systolic hypertension showed that antihypertensive drugs reduce cardiovascular morbidity and mortality^{8,9}, health care professionals who take care of older adults have been often reluctant to provide adequate antihypertensive therapy.¹⁰

Fortunately, a recent studies shed a new light on this gray area. In a meta-analysis¹¹, the Blood

Correspondence to:

Paolo Verdecchia, MD, FACC, FAHA, Struttura Complessa di Cardiologia, Unità di Ricerca Clinica – Cardiologia Preventiva, Ospedale S. Maria della Misericordia, Piazzale G. Menghini, 06132 Perugia, Italy, phone: +39-075-578-22-13; fax: +39-075-578-22-14, e-mail: verdec@tin.it

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Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) compared the effects of different drugs for reducing BP in older and younger adults. A total of 31 trials of more than 190,000 randomized patients were included in the analysis. The reduction in BP levels and the relative risk reduction of a cardiovascular event with various antihypertensive drugs occurred independently of the patients' ages, and the benefits of antihypertensive regimens based on different drug classes were widely comparable across age groups. One potential limitation of this analysis is that the age difference between "younger" and "older" patients was only 15 years, and that 65 years was considered the arbitrary cut-off, even if subsidiary analyses provide reassurance that moderate or large age-related effects had not been missed.¹¹ So, the BPLTTC analysis provides strong support for the use of BP lowering drugs in elderly patients with hypertension.

The HYVET¹², which has been called "the first morbidity/mortality trial to answer the question of antihypertensive treatment in the very elderly hypertensives", is a double-blind, placebo-controlled trial including 3845 patients aged >80 years who had sustained systolic BP (SBP) >160 mmHg or diastolic hypertension (90–109 mmHg). Patients were randomized to either sustained-release indapamide 1.5 mg or placebo. In the first group, perindopril was added as needed. Active treatment, as compared with placebo, was associated to a 64% reduction in the relative risk of heart failure, a 30% reduction in the relative risk of fatal and non-fatal stroke and a 21% reduction in the relative risk of death from any cause.

Therefore, both HYVET and the BPLTTC analysis put the question of the usefulness of treating hypertension in the very elderly to rest, dispelling the suspicion that preventing stroke in these patients might come at the cost of an higher mortality⁶, and signal updates in future versions of the guidelines.

But which is the best drug to treat hypertension in older and younger adults? An age-oriented strategy in the choice of first line antihypertensive drugs is particularly appealing, since it translates a few physiopathological mechanisms, such as the age-related increase in postsynaptic α -adrenoceptor mediated and calcium influx dependent vasoconstriction, as well as the decrease of plasma renin activity, into clinical practice. The recently revised British guidelines¹³ suggest to treat patients below 55 years with angiotensin-converting enzyme inhibitors (ACEI) and older patients with diuretics or calcium channel blockers. On the other hand, the European guidelines¹⁴ underline that evidence for an age-dependent strategy in the choice of antihypertensive drugs is as yet insufficient. In fact, benefits have been demonstrated in older hypertensives for several drug classes, i.e. diuretics, calcium channel blockers, ACEI, angiotensin receptor blockers (ARB) and β -blockers. In the Swedish Trial

in Old Patients with Hypertension (STOP-2), patients randomized to a calcium channel blocker, an ACEI or conventional treatment with diuretics or β -blockers had a similar incidence of cardiovascular events.¹⁵ In the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT), treatment with chlorthalidone, amlodipine or lisinopril reduced cardiovascular events to the same extent even in patients aged ≥ 65 years, although the mean follow-up SBP was 3 mmHg higher in the lisinopril group than in the chlorthalidone group.¹⁶ In the Study on Cognition and Prognosis in the Elderly (SCOPE), that enrolled 4964 hypertensive patients aged ≥ 70 years, randomized to the angiotensin receptor antagonist candesartan or non-ARB antihypertensive treatment, candesartan reduced non-fatal stroke by 27.8%, and all-cause stroke by 23.6%¹⁷; in patients with isolated systolic hypertension, candesartan reduced the risk of stroke by 42%¹⁸. In the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), that randomized 9193 patients aged 55–80 years with essential hypertension and left ventricular hypertrophy, losartan was more effective in reducing cardiovascular events than the β -blocker atenolol; particularly, losartan reduced fatal – and non-fatal stroke by 25%.¹⁹

The BPLTTC analysis did not specifically investigate whether the age-related BP lowering activity of ACEI or ARB differed from that of diuretics or calcium channel blockers. Anyway, the choice of the first drug in older patients often needs to be precisely tailored to individual characteristics, because older adults more frequently have other risk factors, target organ damage and associated clinical conditions (cardiovascular or not) than younger ones. Additionally, many patients will need two or more drugs to control BP, since in the very old may be particularly difficult to obtain a SBP lower than 140 mmHg.^{20,21}

The BPLTTC analysis strongly suggests an early and aggressive management of hypertension irrespective of age; more myocardial infarctions, strokes, heart failures and deaths will be prevented by treating hypertensive patients aged ≥ 65 years than by treating patients ≤ 50 years with the same BP levels.²² Furthermore, according to results from a meta-analysis of HYVET and 3 prior placebo-controlled hypertension trials, presented at the 18th Scientific Meeting of the European Society of Hypertension²³, antihypertensive therapy in elderly patients appears to reduce their risk of dementia by 13% ($p = 0.045$). Finally, clinicians should be aware that antihypertensive treatment should be embedded within the management of global cardiovascular risk, as underlined by the British and European guidelines, with the use of charts for stratifying risk based on additional risk factors (i.e., hypercholesterolaemia and smoking), target organ damage or additional clinical conditions (i.e., diabetes mellitus or a history of cardiovascular or renal disease).

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