

## EDITORIAL



## Treating Hypertension in the Very Old

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Hypertension is prevalent and accounts for a large proportion of cardiovascular morbidity and mortality worldwide.<sup>1</sup> There is a continuous, approximately linear, increase in systolic blood pressure with increasing age in developed and developing nations in both men and women and in most races and ethnic groups.<sup>1,2</sup>

The level of blood pressure is related to the risk of stroke, ischemic heart disease, heart failure, and death from cardiovascular causes (and death from any cause) in a continuous and consistent fashion for values as low as the optimal blood pressure of 115/75 mm Hg.<sup>3,4</sup> For example, among 347,978 men screened for participation in the Multiple Risk Factor Intervention Trial, the risk of fatal stroke for those with systolic blood pressure over 180 mm Hg was about 15 times as high and the risk of fatal ischemic heart disease 7 times as high as the rates among those with optimal blood pressure.<sup>3</sup>

The increase in risk with increasing blood pressure has been found in all age groups, but the strength of the association declines with increasing age, as demonstrated in a meta-analysis of 1 million participants in prospective observational studies.<sup>4</sup> For example, as compared with participants with optimal systolic blood pressure, the rate of death from stroke increases by a factor of 16 for those with a systolic blood pressure of 180 mm Hg among persons 50 to 59 years of age but only by a factor of approximately 3 among persons 80 to 89 years of age. However, the increase in absolute risk is higher in the older age group because of the higher risk at baseline.<sup>4</sup>

Controlled clinical trials carried out in the past five decades have embarked on a path of demonstrating the clinical benefit of treating different subgroups of patients with hypertension. The Hypertension in the Very Elderly Trial (HYVET), re-

ported on by Beckett et al.<sup>5</sup> in this issue of the *Journal*, shows a benefit in treating the very old and is an important next step in this journey. In his 1937 textbook, the eminent cardiologist Paul Dudley White wrote that “the treatment of the hypertension itself is a difficult and almost hopeless task in the present state of our knowledge, and in fact for aught we know, in advanced cases with permanently narrowed coronary and cerebral arteries the hypertension may be an important compensatory mechanism which should not be tampered with.”<sup>6</sup> The “present state of our knowledge” has advanced a lot, beginning with the demonstration in 1967 of a clinical benefit of antihypertensive therapy in the Veterans Administration Cooperative Group of patients with severe hypertension (diastolic blood pressure, 115 to 129 mm Hg).<sup>7</sup> Since that time, clinical trials have shown a benefit in treating less severe degrees of diastolic hypertension, isolated systolic hypertension, and hypertension in older persons. A quantitative overview of controlled clinical trials involving more than 160,000 patients, with 700,000 patient-years of follow up, indicates that treatment with any commonly used regimen to lower blood pressure reduces the risk of major cardiovascular events and that larger reductions in blood pressure result in larger reductions in risk.<sup>8</sup>

In HYVET, a double-blind, randomized, placebo-controlled clinical trial involving 3845 patients 80 years of age or older with hypertension, Beckett et al. evaluated the effect of stepped-care therapy, beginning with indapamide and adding perindopril as needed. The authors found that active treatment, as compared with placebo, was associated with a 21% reduction in the relative risk of death from any cause, a 64% reduction in the relative risk of heart failure, and a 30% reduction in the relative risk of stroke.

In the presence of previous overwhelming evidence in favor of antihypertensive drug therapy, why was HYVET necessary? In addition to the attenuation of the relative risk imposed by hypertension, there were concerns related to the inverse epidemiologic association of death from any cause and blood pressure in the very old and about the efficacy and safety of antihypertensive drug therapy in this age group. There was speculation that impaired cardiac, renal, and baroreceptor function, as well as orthostatic hypotension, cognitive impairment, subjective side effects, and polypharmacy (with its increased risk of drug interactions), would detract from the clinical benefit of antihypertensive treatment in the very old. In addition, a meta-analysis of clinical-trial participants 80 years of age or older, carried out by the Individual Data Analysis of Antihypertensive Drug Interventions (INDANA) group, showed no beneficial effect on the risk of death from any cause (with a 6% increase that was not significant) in spite of the decrease in the risk of cardiovascular events.<sup>9</sup>

The lack of definitive data on the advisability of treating hypertension in persons 80 years of age or older is reflected in the U.S. and European guidelines on management of hypertension. HYVET puts the question of the usefulness of treating hypertension in the very old to rest and provides important guidance to physicians and writers of such guidelines.<sup>5</sup> A significant and clinically important decrease in the rates of death from any cause and of fatal or nonfatal heart failure was found at a median of 1.8 years of follow-up. Although in the intention-to-treat analysis, the decrease in the risk of any stroke did not reach nominal significance, the study was stopped prematurely for ethical reasons at the advice of an independent data monitoring committee, owing to the significant benefit of active therapy with regard to death from any cause. Although it is unfortunate that the stopping rules for this eventuality were not established a priori, it would have been difficult to continue the study in the presence of a clear effect on death from any cause.

The investigators and, apparently, the data monitoring committee considered this finding to be unexpected. Beckett et al. propose a plausible explanation for the more pronounced effect of HYVET on total mortality. The proportion of strokes that were fatal in HYVET was higher than

that in previous studies of younger individuals. Nevertheless, the observed relative risk reduction in total mortality is within the 95% confidence intervals of the relative risk reduction reported in other studies of hypertension in the elderly (Swedish Trial in Older Patients with Hypertension, the Systolic Hypertension in the Elderly Program, and the Systolic Hypertension in Europe trial). Thus, the findings of HYVET are consistent with those of previous trials and indicate an overall significant benefit of the treatment of hypertension in the very old.

In applying the findings of this trial, we should keep in mind that the patients in HYVET were healthier than normal for their age. Aging affects people to various degrees, depending on inherited characteristics, lifestyle, and disease. Like all clinical trials, those involving old persons with hypertension must also involve individualized treatment that takes into account the factors that are associated with aging as well as individual preference.

The results of HYVET prove that it is not too late to start antihypertensive therapy in older people and expands the upper limit of the age spectrum for which there is evidence from clinical trials of a treatment benefit. The question of the benefit, risk, and expense associated with therapy for young, low-risk patients who may need treatment for decades deserves attention. Current practice is based on incomplete evidence as well as speculation.<sup>10</sup> The HYVET investigators deserve to be congratulated for persevering and ultimately succeeding in proving the benefit of treating hypertension in the very old.

Dr. Kostis reports receiving consulting fees from Pfizer and Sankyo-Forest and grant support from Boehringer Ingelheim and Pfizer. No other potential conflict of interest relevant to this article was reported.

This article (10.1056/NEJMMe0801709) was published at [www.nejm.org](http://www.nejm.org) on March 31, 2008.

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