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Review Article

Embracing Complexity: A Consideration of Hypertension in the Very Old

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The consequences of hypertension and its treatment differ in very old men and women compared to younger populations. In populations aged 85 years and older, higher levels of systolic and diastolic blood pressures are associated with increased survival, and this relationship is not eliminated by controlling for comorbidity, blood pressure treatment, and other relevant factors. In addition, in 3 of the 4 published randomized controlled trials of treatment of hypertension that included subjects aged 80 years or older, the investigators reported loss of efficacy of treatment in preventing the primary end points in subjects aged 80 and older. In a meta-analysis of those trials, total mortality was actually 14% higher ($p = .05$) in the treatment group for subjects aged 80 years and older. These data suggest 2 conclusions. First, we should reexamine that dictum that nontreatment of hypertension in those aged 80 years and older is de facto evidence of "ageism." Second, we are unlikely to come to any set of coherent "rules" regarding treatment of hypertension (and several other conditions) in the very old until we routinely stratify all older subjects enrolled in interventional or observational trials by indicators of physiologic vigor.

THIS essay was stimulated by an article (1) and accompanying editorial (2) in this Journal on treatment of hypertension in the elderly. In the article, the authors found that at any given level of high blood pressure (e.g., systolic of 140, 160, 180), the geriatricians surveyed were less likely to initiate pharmacological treatment in an 85 year old than in a 65 year old. The authors concluded that there was "an urgent need to improve health care providers' " opinions about target blood pressure in the elderly hypertensive patient" (1). The accompanying editorial concluded that "we cannot justify an age threshold beyond which hypertension should not be treated" (2).

My motives for writing this essay are complex, so I will try to sort them out at the outset. First, I disagree with the conclusions of the articles cited above. They ignore a large body of work showing that elevated blood pressures are associated with improved survival in men and women aged 80 and older. In addition, trials of treatment of hypertension in those aged 80 and older report outcomes favoring placebo over drug therapy. These studies will be reviewed below.

My second motive in writing is that the rules we have for conducting discussions about whether or not one should do treatment X for condition Y do not work when the population under consideration is very old. To ignore that fact does violence to the reality facing practitioners who care for these populations. In other words, we need a new paradigm in which to exchange information about appropriate care of the very old. A careful consideration of implications of what we actually know about hypertension in those aged 80 and older will both illustrate the very real limits of our current model and suggest alternative models for consideration.

Consequences of Hypertension

The justification for treating an asymptomatic condition in any population rests on 2 tenets. First, the condition must be associated with increased risk of subsequent adverse health events. Second, treatment of the asymptomatic condition must cause more good than harm; those treated should on average experience better outcomes than those not treated. The treatment of hypertension clearly meets both conditions. Indeed, national programs to recognize and treat hypertension have been credited with much of the reductions in stroke and stroke mortality over the last few decades of the 20th century (3).

What about old people with high blood pressure? I will not review the data on the risks from hypertension and the benefits of treatment of hypertension in the age 65 and older population, because I would imagine that almost all readers are familiar with that literature. Let me summarize by stating that the risks from any given level of hypertension, and the benefits of treating such hypertension, both increase substantially with age. In other words, a physician prevents more strokes, heart attacks, episodes of heart failure, and deaths by treating 1000 men and women aged 65 and older than one would by treating 1000 50 year olds with the same level of high blood pressure (3).

What about very old people? I will use age 80 as a cut-off for defining "very old," recognizing that the use of such an arbitrary point is a reflection of the limits of our current model of generating "rules" for geriatrics, to be discussed later.

To summarize my argument, neither criterion for the treatment of an asymptomatic condition is met with hypertension in the very old. First, high blood pressure is not associated with adverse health outcomes. To the contrary, it

Table 1. Five-Year Mortality by Level of Systolic or Diastolic Blood Pressure at Entry, in 2 Population-Based Studies of Those Aged 85 and Older

Systolic BP	Percent Alive at 5 Years		Diastolic BP	Percent Alive at 5 Years	
	Leiden	Tampere		Leiden	Tampere
90–120	15	5	50–69	12	(*)
>120–140	25	14	60–69	26	8
>140–160	39	29	70–79	31	19
>160–180	36	40	80–89	34	31
>180–200	31	39	90–99	35	39
>200	41	44	100–109	(**)	35
			>110	41	46

Notes: * In the Tempere study ($n = 561$), the lowest category of diastolic blood pressure was <70 (4).

** In the Leiden study ($n = 833$), the highest category of diastolic blood pressure was >100 (5).

is a marker for survival, among the most powerful markers available to the clinician. Second, treatment does not seem to help. On the contrary, it may cause harm. I will first review the epidemiologic evidence addressing the first point, and then the clinical trial evidence addressing the second.

Hypertension Is Associated With Good Outcomes for the Very Old

Table 1 summarizes the results of 2 population-based studies of the relationship of systolic and diastolic blood pressure level and 5-year mortality in men and women aged 85 and older. One study (4) enrolled 83% of the 85-years-and-older population of Tempere Finland (561 subjects) and the other (5) enrolled 94% of the 85-years-and-older population of Leiden, the Netherlands (833 subjects).

In both studies the chance of being alive at 5 years for subjects with high or very high blood pressures were several-fold greater than for those with "normal" systolic blood pressures. For example, in the Tempere study, those with systolic pressures ≥200 mmHg on entry had a threefold higher chance of surviving 5 years than did those with systolic pressures of 120–140 mmHg. In the Leiden study, subjects with systolic blood pressures of >200 were 64% more likely to be alive 5 years later than those subjects with blood pressures in the 120–140 range.

Similar results were reported by the Helsinki Aging study, which followed a population-based sample of 174 80 year olds and 146 85 year olds for 5 years (6). In that study, the adjusted risk ratio for 5-year mortality declined 10% for every 10-mm increase in systolic blood pressure at entry, and declined 8% for every 5-mm increase in diastolic blood pressure.

In addition to the 3 studies summarized above, there are 2 earlier population-based or community-based studies reporting data on blood pressure and survival for subjects aged 85 years and older (7,8), and both report results consistent with the results described above.

Other population-based studies have examined the relationship of blood pressure to survival in those aged 80 and older or aged 75 and older (9–20). The inverse relationship between blood pressure and mortality is still found, but not with the consistency of the studies on the 85-years-and-older populations. Some of these studies reported that the paradoxical relationship of blood pressure and mortality in very old populations was stronger in men than in women (9,20). Sometimes there is no relationship between blood pressure and mortality. No study has reported that elevated systolic or diastolic blood pressure predicts increased mortality in a population aged 80 years and older. One good example is the Framingham study (13), which provided the best early evidence for increased adverse consequences of hypertension with increasing age. The Framingham study found a positive linear relationship between blood pressure and cardiovascular mortality both in the younger (35–64 years) and older (65–84 years) population, with a steeper slope in the 65- to 84-year-old group. But when the sample was broken into 4 age groups (45–54, 55–64, 65–74, and 75–84), the positive association between blood pressure and cardiovascular mortality was seen only up to the 65–74 age group. In the 75–84 age group, the systolic and diastolic blood pressures were inversely associated with cardiovascular mortality among both men and women (13).

Other studies have examined the relationship of levels of blood pressure and health indicators other than mortality (21–23). For example, we found that subjects with levels of systolic pressure <120 were significantly more likely to report somatic and depressive symptoms, after controlling for other factors that might affect health (21).

Before we move on to discuss potential explanations for the data shown in Table 1, it would be useful to pause and consider the implications of those data, because many of the implications will be the same regardless of the mechanism(s) responsible for the phenomenon. The most striking implication is that high blood pressure is a marker for survival in the 85-and-older populations. Put another way, when confronted with an 88-year-old patient, the clinician should be happy to find, for example, a blood pressure of 200/100. That individual has a substantially greater chance of survival than if his or her blood pressure were 130/70. The reader should perhaps consider what his or her actual response to a blood pressure of 200/100 in an 88 year old would be. Conversely, a blood pressure of, for example, 120/70 in a 90 year old is a poor prognostic sign. This concept may make some readers uncomfortable, but that discomfort does not relate to the validity of the observation. The association of elevated blood pressure with increased survival in the very old is well supported by the evidence.

Outcomes of Antihypertensive Therapy in the Very Old

Because elevated blood pressures among the very old are not associated with bad outcomes, one might argue that the question of whether very old subjects with elevated blood pressures should be "treated" with antihypertensives is nonsensical. Nevertheless, given the very real benefits of the treatment of hypertension in younger populations, it is reasonable to postulate that such benefits could extend to the very old. In other words, even though high blood pressure is associated with increased survival, perhaps treating very old subjects with high blood pressure results in even better outcomes.

Table 2. Subgroup Meta-Analysis of Outcomes of Antihypertensive Treatment in 1566 Subjects Aged 80 and Older Enrolled in 5 Double-Blind Trials, Followed for an Average of 3 Years

Outcome	Number of Events		Relative Risk (95% Confidence Interval)**
	Treatment ($n = 824$)	Control ($n = 742$)	
Stroke*	51	69	0.64 (0.40, 0.89)
Coronary events*	39	41	0.85 (0.48, 1.32)
Heart failure*	33	50	0.58 (0.37, 0.90)
Cardiovascular deaths	104	93	1.11 (0.87, 1.41)
All deaths	208	180	1.14 (1.00, 1.31)

Notes: * For stroke, coronary events and heart failure, data were unavailable from EWPHE.

** Data are taken from Gueyffier et al. (28). The 95% confidence intervals were estimated from Figures 1 and 2 in Ref. 28.

Table 3. Summary of 2 Meta-Analyses of Outcomes of Antihypertensive Treatment: One Comprising 1566 Subjects Aged 80 and Older and the Other Comprising 15,693 Subjects Aged 60 and Older

Outcome	Relative Risk (95% Confidence Interval)	
	Subjects 80 years*	Subjects 60 years**
Stroke	0.64 (0.40, 0.89)	0.70 (0.59, 0.82)
Coronary event	0.85 (0.48, 1.32)	0.77 (0.66, 0.90)
Cardiovascular death	1.11 (0.87, 1.41)	0.82 (0.71, 0.96)
All death	1.14 (1.00, 1.31)	0.87 (0.68, 0.98)

Notes: * Data taken from Gueyffier et al. (28).

** Data taken from Staessen et al. (29). The two meta-analyses were performed by the same group of investigators (28,29), with similar analytic approaches. The 1566 subjects included in the meta-analysis of subjects aged ≥80 years are also included in the meta-analysis of subjects ≥60 years.

The efficacy of antihypertensive therapy in very old people has been addressed in several of the larger trials of treating hypertension in older men and women; i.e., older than 60, 65, or 70 years of age. Three of the 4 trials that have examined the effect of treatment in those aged 80 years and older have reported a significant interaction between age and treatment effect, whereby the benefits of treatment on survival is eliminated or reversed in subjects aged 80 years and older. The Swedish Trial in Older Patients with Hypertension (STOP–Hypertension) enrolled subjects aged 70 to 84 years with systolic blood pressures between 180 and 270 or diastolic pressures between 105 and 120 mmHg (24). Treatment was associated with substantial reductions in risk of cardiovascular events ($RR = 0.60$). However, a Poisson analysis of benefit of treatment versus age of the subjects treated showed decreasing benefit of treatment with increasing age, with the curve of relative risk crossing unity between age 80 and 85 (24). In the European Working Party on Hypertension in the Elderly (EWPHE), there was a significant treatment × age interaction, with no benefit of treatment in those over age 80 (25). A similar treatment × age interaction was reported for the European Trial on Isolated Systolic Hypertension in the Elderly (Sys-Eur) (26). In that study, total mortality and cardiovascular mortality were both substantially decreased in the treatment group under age 80, but not in those aged 80 years and older. For example, the hazard rate for total mortality was 0.58 among those in the treatment group aged 70–74 years while it was 1.11 for those aged 80 years and older.

On the other hand, the Systolic Hypertension in the Elderly (SHEP) trial reported that the effect of antihypertensive treatment on reducing strokes was at least as great in subjects aged 80 years and older as it was for subjects 60 to 80 years of age (27). Other outcomes, such as cardiac and all-cause mortality, were not reported separately for those aged 80 and older by SHEP.

Gueyffier and colleagues (28) conducted a subgroup meta-analysis of 5 double-blind trials of antihypertensive treatment that included subjects aged 80 years or older (SHEP, the pilot study for SHEP, STOP, EWPHE, and Sys-Eur). These results are summarized in Table 2, for 824 actively treated and 742 placebo subjects aged 80 years or older, followed for an average of approximately 3 years. Two patterns are apparent. First, treatment was associated with significantly reduced risks of stroke and heart failure. Second, mortality was higher in the treated group. This was true for cardiovascular mortality, where there was an 11% higher risk of death in the treatment group compared with placebo ($p = .42$) and for total mortality where the excess risk of death experienced by the treatment groups was 14% ($p = .05$). Thus antihypertensive treatment in those aged 80 and older was associated with reductions in risk of stroke and heart failure but an increase in total mortality.

We can compare these results of subjects aged 80 years and older to those reported in a meta-analysis of 8 antihypertensive trials of subjects aged 60 years and older (Table 3) (29). The degree of reduction in stroke associated with treatment was roughly comparable in the 2 age groups. However in the meta-analysis of trials enrolling subjects aged 60 years and older, treatment was associated with a 13% reduction in total mortality ($p = .02$) compared to a 14% increase in mortality in the meta-analysis of trials with subjects aged 80 years and older ($p = .05$). Interestingly, the subjects in the subgroup meta-analysis aged 80 years and older were included in the meta-analysis of subjects aged 60 years and older. Thus, the decreased mortality associated with treatment reported in the meta-analysis of subjects aged 60 years and older must have been greater than 13% for the subgroup of subjects aged 60 to 79 years.

There is one additional point to make from these data. Because the underlying death rate of the 85-years-and-older population is many-fold higher than in the aged 65–74 years population (Table 4), the absolute increase in deaths associated with antihypertensive treatment of those 85 years and older would be several-fold higher than the absolute reductions in deaths from treating younger populations, if we assume the findings of the randomized clinical trials are correct.

The Hypertension in the Very Elderly Trial (HYVET), which has yet to report its results, is as large as the meta-analysis of the 5 trials shown in Table 2. This trial will report on quality of life indicators as well as mortality (30). Thus, the quantity and quality of information on effects of treatment in those aged 80 years and older will increase considerably when those results are published.

Table 4. Death Rates and Prevalence of Disability by Age Group for the United States, 1999*

Age (y)	Deaths/1000 persons/y	Percent Disabled**
35–44	1.9	
45–54	4.3	
55–64	10.0	
65–74	24.8	8.4
75–84	57.5	21.4
85+	154.8	52.7

Notes: * Data on death rates are from National Vital Statistics System, CDC/NCHS. Data on disability are from Manton et al. (41).

** Percent disabled include those institutionalized or impaired in activities of daily living.

What Is the Explanation for These Findings?

In searching for mechanisms to explain the unusual findings reviewed thus far, I will address 2 questions separately:

1. Why does elevated blood pressure predict survival in the very old?
2. Why do attempts to lower elevated blood pressures in the very old result in excess mortality?

Why Does Elevated Blood Pressure Predict Survival in the Very Old?

The potential explanations for this phenomenon are of 2 types:

1. Elevated blood pressure in the very old is a marker for physiologic vigor; or
2. Elevated blood pressure is good for very old people; it may be necessary, for example, to maintain perfusion of vital organs.

This available evidence would suggest that both explanations have validity.

The first postulated explanation could be stated as follows. The rapid rise in prevalence of hypertension with advancing age reaches a plateau at about age 70. The reason why the prevalence of hypertension does not continue to rise with age over age 70 is because of the high prevalence of cardiovascular disease and other serious comorbidities in older subjects. Thus, older subjects with "normal" blood pressures are comprised of 2 populations: those with truly normal blood pressures and those where the normal pressure is a product of a failing cardiovascular system in individuals who would otherwise have elevated pressures. The older the population, the greater the proportion of normotensives attributable to comorbidity.

Several lines of evidence support this explanation. First, we (31) and others (11,14) have shown that declines in blood pressure levels over time predict increased mortality. Presumably, some underlying comorbidity, detected or undetected, was responsible both for the decline in blood pressure and the subsequent mortality. Second, the association of elevated blood pressures and lower mortality in older populations is reduced after excluding deaths in the first few years of follow-up and controlling for comorbid conditions. This is especially true in somewhat younger populations. Several longitudinal studies of 65-and-older or 70-and-older populations have found positive associations between levels of blood pressure and survival that were eliminated or were reversed after controlling for comorbidity (16–18,32). However, including such controls in the analyses does not eliminate the association of hypertension with survival in very old populations (6,10,33). For example, we examined the relationship between blood pressure and 6-year survival among 1088 individuals aged 85 and older enrolled in 4 sites of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) (33). In analyses adjusted for age, functional status, medication use, medical diagnoses, cognitive function, and gender, there was a strong positive association between level of systolic blood pressure and survival in men, with each 10-mmHg increase in blood pressure associated with an 8% decrease in hazard of death over a 6-year follow-up. When subjects were stratified by whether or not they were taking antihypertensives, the association was found in both groups. Of interest, there was no relationship between blood pressure and survival in women aged 85 and older.

In summary, the concept of hypertension as a marker for physiologic vigor may partially explain the association of hypertension and enhanced survival in the very old, but it is not the complete explanation. For one thing, it would not explain the increased mortality associated with treatment of hypertension of the very old in the clinical trials (Table 2). This leads us to consider the second possible explanation, that elevated blood pressure is good for very old people. This will be discussed below.

Why Do the Clinical Trials Report Excess Deaths From Treatment of Blood Pressure in Very Old People?

We can approach this question in several ways. First, consider the death rates by age given in Table 4. In an 85-and-older population, 155 per 1000 people will die each year. If one looks at the estimates of reductions in mortality from antihypertensive treatment in younger populations, they are dwarfed by the average death rate in the 85-and-older population. For example, in the meta-analysis of trials of antihypertensive treatment in subjects aged 60 and older, the 13% reduction in mortality ($p = .02$) in the treatment groups translates to an absolute reduction in mortality of 3.4 deaths per 1000 per year (29). This absolute reduction in total mortality of 3.4 per 1000 per year would have a far greater relative benefit in a 65- to 74-year-old population, with an underlying mortality rate of 25 per 1000 per year (indeed, it is very close to the 13% reduction in mortality reported in the meta-analysis) than in a population of individuals 85 years and older with an underlying mortality rate of 155 per 1000 per year. Thus, even if antihypertensive treatment had the same absolute benefit to mortality in those 85 years and older as in those 60 years and older, it would be difficult to detect, given the much higher underlying death rate of the very old population.

But that does not explain the increase in mortality associated with treating hypertension in very old people; it only explains why any benefit might be difficult to document. To explain the increase in mortality, we have to postulate that

there are competing benefits and harm from elevated levels of blood pressure or from lowering those elevated levels with medications, and that in very old age, the benefits outweigh the harm. Why might that be? Perhaps there is selective attrition, with those most susceptible to the harmful effects of hypertension dying off by age 80. Alternatively, perhaps high blood pressure has more benefit in very old populations. Perhaps it is required to maintain perfusion. Perhaps it is a homeostatic adjustment that actuality has survival value. Port and colleagues (34) recently published a thoughtful reanalysis of the Framingham data, suggesting that the cut point for what should be considered systolic hypertension rises steadily from age 45 to 75. Also, there is substantial literature from the controlled trials showing that subjects whose blood pressures are reduced below certain levels (e.g., <85 diastolic) experience worse outcomes than do untreated subjects (35–37).

Another possible explanation is that the drugs used to treat hypertension might have a different spectrum or magnitude of serious toxicities in the very old. Perhaps there is a class of serious toxicities from antihypertensives in very old people that has not been recognized thus far. Certainly it is difficult to recognize serious drug toxicity in a population with an underlying death rate of 150 per 1000 per year.

How Should We Approach Very Old People With Hypertension?

Medicine is practiced in a cultural context (38). One of the tenets of our culture is that high blood pressure is bad. In my experience, levels of systolic blood pressure greater than 200 are often viewed by medical personnel as a medical emergency. Thus, the geriatrician who does not treat such patients risks many calls from, for example, ophthalmologists' offices or grandchildren who are physicians. At a minimum, however, the geriatrician can share the news that such levels of blood pressure are a good prognostic sign.

It is important to remember that cultures change, sometimes dramatically. Our recent about-face on postmenopausal estrogen supplementation is the most recent example of this. I am not arguing that the medical community should perform a similar about-face in its approach to hypertension in the very old, based on the evidence reviewed thus far. I am arguing that we should acknowledge our lack of understanding about this issue.

Recognition of the complexities in thinking about hypertension in the very old can be a powerful means of stimulating important new clinical research. If most very old people with "normal" blood pressures have those levels because of underlying cardiovascular disease, perhaps it is they who would benefit most from therapy with an angiotensin inhibitor. Perhaps there are dramatic differences in outcomes among very old hypertensives, depending on the antihypertensive agent used (e.g., angiotensin inhibitor vs diuretic).

Do We Need a New Paradigm to Talk and Think About Very Old Age?

An axiom of gerontology is that physiologic aging is as important as chronologic aging. Very old age is a period of exceptional physiologic heterogeneity, as evidenced by the data in Table 4. Perhaps we should make no age-based rules in subjects over age 80. Just as the founding aphorism of medicine is "First do no harm," perhaps the central theme of geriatrics should be "no finding in isolation." No fact about a person 80 years or older can be considered unless it is given in the context of that individual's physiologic condition.

Another implication of the extreme heterogeneity in very old age is that multivariate statistical models are not appropriate analytic tools with which to study this population. The late Alvan Feinstein warned that the mathematical models that evolved in the social sciences actually distort the realities facing the clinician, and impede progress in developing clinically relevant information (39). Nowhere is this more true than with the very old. What does it mean, for example, to say that, after controlling for potential confounders, level of blood pressure predicts survival in the very old? Diehr and colleagues (40) recently noted that very old populations represent a mixture of those who are aging and those who are dying. How can we analyze this population with approaches that produce findings that start with the phrase "on average," such as "on average, blood pressure level predicts survival." What average? What is an average 90 year old? Similarly, how can we interpret a statement such as "after controlling for functional status, X predicts Y in very old people"? How does one "control" for functional status in a population where many are institutionalized and many others are fully functional? How can the result of any such analysis be interpretable?

A formal test for significant interactions would be an imperfect method to salvage a methodology that should not have been applied in the first place. A better approach would be to forego the use of multivariate techniques in older populations. It would be more useful to attempt to define more homogeneous subpopulations among very elderly persons.

There are many ways to define potential categories of very old individuals, such as age, walking speed, level of cognition, ejection fraction, level of affect, and self-rated health. All predict survival in the very old. Perhaps the only way we can successfully approach the question of whether treatment X is good for condition Y in the very old is to always insist from the outset that the question be limited to more narrowly defined cohorts of older persons, based on easily obtainable physiologic measures. Alternately, post hoc subgroup analyses of clinical trials, a technique with obvious hazards, is a powerful tool to understand different patterns of response to treatment. With such approaches, we may eventually be able to understand the exceedingly complex issue of hypertension in the very old. Until that time, it will be difficult to fault clinicians for either treating or not treating very old people with high blood pressure.

Acknowledgment

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