Dr. Nicastrì reports receiving lecture fees from GlaxoSmithKline; Dr. Narciso, lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, and GlaxoSmithKline; and Dr. Andreoni, lecture and consulting fees from Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Pfizer, Merck, Roche, and Tibotec. No other potential conflict of interest relevant to this letter was reported.


THE AUTHORS REPLY: Schulz and Street request specific causes of death to determine whether there were associations according to treatment group. There was no significant difference in the time to death among the three treatment groups ($P>0.24$ for the overall comparison). Of 19 deaths (9 in the efavirenz group, 3 in the lopinavir–ritonavir group, and 7 in the NRTI-sparing group), 6 deaths were potentially HIV-related (those due to infection, cancer, and myelopathy), and 6 were non-AIDS-defining events (2 related to cancer and 1 each to cardiac, respiratory, hepatic, and infectious disorders); the 7 remaining deaths were not disease-related (i.e., accidents and non–HIV-drug-related overdoses). The varied causes of death and their infrequency make it difficult to discern differences in the patterns of death across the treatment groups.

Nicastrì and colleagues inquire about the effect of a low baseline CD4 cell count on the virologic outcome according to treatment group. There were no significant between-group differences in the time to virologic failure among patients with a baseline CD4 cell count of less than 100 cells per cubic millimeter. The proportions of patients without virologic failure at 96 weeks were 69% (95% confidence interval [CI], 59 to 79) in the efavirenz group, 66% (95% CI, 55 to 76) in the lopinavir–ritonavir group, and 64% (95% CI, 54 to 74) in the NRTI-sparing group.

We would like to clarify some points made by Hirschel and Calmy in the editorial\textsuperscript{1} that accompanied our article. Specific NRTI agents were not assigned by the protocol; they were selected by the site investigator for each patient. The development of extended-release stavudine was halted because of manufacturing difficulties, not because of an increased risk of pancreatitis. In addition, the editorial states initially that limitations of our study “cast doubt on the future applicability of the study’s findings” but then concludes that the study results “challenge the 40% of clinicians who start antiretroviral therapy with a protease inhibitor. . . .” We agree that the study results should alter recommendations for optimal initial therapy of HIV-1 infection, which was its intent.

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**Treatment of Hypertension in the Elderly**

**TO THE EDITOR:** In his editorial accompanying the article by Beckett et al.,\textsuperscript{1} on the results of the Hypertension in the Very Elderly Trial (HYVET), Kostis (May 1 issue)\textsuperscript{2} describes why he thinks the data from the study are important. However, the vast majority of patients who were enrolled in the trial (3670 of 3845) came from Eastern Europe and China; only 105 were recruited from Western countries. Since Eastern European and Chinese populations have an increased rate of death from stroke by a factor of as much as 10 (Table 1), we wonder whether the beneficial effects of antihypertensive therapy in the “high-risk, stroke-prone” Eastern populations apply in “low-risk” Western populations. Furthermore, there appears to be a recruitment bias, since 43 investigators recruited 2144 patients in Eastern Europe, but 93 investigators recruited only 86 patients in Western Europe.

The study included two different populations with respect to the use of antihypertensive drugs. The majority of patients were already receiving antihypertensive drugs, and about one third initiated drug therapy during the study. Although an overall treatment benefit is reported in the study, we believe it is crucial to know the findings in the two subgroups, since it is otherwise
uncertain whether it is beneficial either to continue or to initiate drug therapy or whether the two approaches are equally effective in patients who are 80 years of age or older.

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TO THE EDITOR: The HYVET investigators used vigorous exclusion criteria to define their study population but did not report the percentage of screened patients who passed muster. Elderly patients with hypertension commonly present with multiple coexisting illnesses that exclude them from participation in clinical trials. Of every 100 patients who were contacted in the Systolic Hypertension in the Elderly Program (SHEP) trial, 12 met the initial study criteria, 3 completed a baseline visit, and only 1 underwent randomization.

We applied the published exclusion criteria from the HYVET and SHEP studies and from 11 other randomized clinical trials — the Australian National Blood Pressure Study 2, Metoprolol in Elderly Hypertensive Patients, Medical Research Council Trial of Treatment of Hypertension in Older Adults, European Working Party on High Blood Pressure in the Elderly, Effects of Amlopidine and Lisinopril on Left Ventricular Mass, Study on Cognition and Prognosis in the Elderly (SCOPE), Swedish Trials in Old Patients with Hypertension 1 and 2 (STOP Hypertension 1 and 2), Systolic Hypertension in Europe, Systolic Hypertension in the Elderly: Long-term Lacidipine (SHELL), and Hypertension in Elderly Patients (HEP) — involving elderly patients with hypertension to a Polish cohort of 5530 patients with hypertension who were over the age of 60 years and were recruited from general practices. A total of 3944 patients (71.3%) met at least one exclusion criterion, and the proportion of patients who would have been excluded in the studies mentioned above ranged from 41.1 to 76.6%. Trial-eligible patients were remarkably healthy, as compared with those who were excluded (Table 1).

Patients in clinical trials, such as those in Table 1. Rates of Death from Stroke in Eastern and Western Countries.\(^*\)

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of Deaths per 100,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern</td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>453</td>
</tr>
<tr>
<td>Romania</td>
<td>251</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>227</td>
</tr>
<tr>
<td>China</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>243</td>
</tr>
<tr>
<td>Urban</td>
<td>217</td>
</tr>
<tr>
<td>Western</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>35</td>
</tr>
<tr>
<td>Canada</td>
<td>28</td>
</tr>
<tr>
<td>Australia</td>
<td>30</td>
</tr>
<tr>
<td>New Zealand</td>
<td>40</td>
</tr>
<tr>
<td>Germany</td>
<td>39</td>
</tr>
<tr>
<td>France</td>
<td>35</td>
</tr>
<tr>
<td>Italy</td>
<td>41</td>
</tr>
<tr>
<td>England</td>
<td>49</td>
</tr>
</tbody>
</table>

\(^*\) Data are from the American Heart Association for 2008. Rates of death from stroke in the listed countries are similar to those in 2003 and thus are applicable to the period studied in the Hypertension in the Very Elderly Trial.

Table 1. Eligibility for Participation in Clinical Trials among 5530 Elderly Polish Patients, According to Criteria from 13 Trials Involving Elderly Patients with Hypertension.\(^*\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ineligible Patients</th>
<th>Eligible Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>3944 (71.3)</td>
<td>1586 (28.7)</td>
<td></td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>69.3±6.4</td>
<td>67.1±5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>57.0</td>
<td>62.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of early cardiovascualr disease (%)</td>
<td>34.7</td>
<td>22.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>76.3</td>
<td>71.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal obesity (%)</td>
<td>61.7</td>
<td>55.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (%)</td>
<td>37.5</td>
<td>21.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary heart disease (%)</td>
<td>49.2</td>
<td>19.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>20.0</td>
<td>2.1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\(^*\) Plus–minus values are means ±SD.
HYVET, are not representative of the majority of elderly patients with hypertension. Evidence that is gathered in such trials should be applied cautiously in clinical practice.

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TO THE EDITOR: In the study by Beckett et al., we note the small number of undefined “serious adverse events,” of which only five were judged to be probably associated with study medications. Although the authors report that serious adverse events were more common in the placebo group than in the treatment group, the details of these adverse events are not presented. In particular, neither orthostatic hypotension nor hyponatremia that limited the use of study drugs is mentioned.

The prevalence of orthostatic hypotension in healthy elderly persons has been estimated at 5 to 30%, and patients taking antihypertensive agents have even higher rates. Orthostatic hypotension is associated with an increased risk of cardiovascular events, falls, fractures, and death. In addition, normal physiological changes of aging result in impaired water homeostasis and increased susceptibility to drug-induced hyponatremia, which can have serious adverse outcomes.

The goal of preventing strokes and death from cardiovascular causes in elderly patients should be considered in the context of the possibility of an increased risk of adverse drug-related events, which in practice often limits the use of antihypertensive medications.

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THE AUTHOR REPLIES: We did not perform population screening in our study. Patients were selected by local investigators from among patients attending their clinics, some of which were sited in primary care settings and some in secondary care settings. Prescreening details were not recorded routinely by investigators. As in most other trials, patients who were recruited to participate in our study were healthier than persons of similar ages within a general population. For example, patients with a diagnosis of dementia were excluded, and up to 20% of persons who are 80 years of age or more have evidence of dementia. However, the number of 80-year-olds who are healthy is increasing, so it will be important to take steps to ensure that they remain so. HYVET showed no
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The data supplied by Messerli et al. may not provide an appropriate comparison with our results, since the vast majority of their patients appear to be under the age of 80 years. Those who reach 80 years are, by definition, survivors.

As noted by Cheah and Wilson, side-effect profiles and safety are important considerations in regard to potentially long-term pharmacologic interventions, particularly in the elderly, who have adverse drug reactions more commonly than younger patients. In our study, there were fewer serious adverse events in the group that received indapamide than in the placebo group. Data on other adverse events were not routinely collected. Preliminary analyses revealed nonsignificant differences in serum sodium levels between the two groups in the 2-year cohort and no increase in orthostatic hypotension, although the majority of patients were receiving treatment with a combination of indapamide and perindopril at 2 years.

The performance of subgroup analyses and the extrapolation of data from such studies always arouse concern. There were too few patients who were recruited from Western Europe and the follow-up of Chinese patients was too short to allow for comparisons on the basis of country. However, the combination of being 80 years of age or older and having hypertension already puts a person at high risk for a future cardiovascular event, and HYVET showed positive benefits with regard to cardiovascular events. A history of treatment for hypertension was not a criterion for assignment to a prespecified subgroup and was not analyzed as such.

Sutton asks whether it was ethical to include patients who had already had a stroke or myocardial infarction in our study. Evidence of a benefit in patients who are 80 years of age or more is very scanty and has accrued since the trial was started. In the Perindopril Protection against Recurrent Stroke Study (PROGRESS), patients were much younger than those in our study. A history of cardiovascular disease was a criterion for assignment to a prespecified subgroup and will be addressed in future analyses of HYVET data.

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Keratoderma Blennorrhagica–like Rash

TO THE EDITOR: Tonna and Laing (May 15 issue) describe a patient with secondary syphilis. I question the authors’ use of the term “keratoderma blennorrhagica,” which are the psoriasiform and vesicular pustular lesions of the palms and soles seen in Reiter’s syndrome, along with symptoms involving the joints, eyes, and urinary tract. Although similar, the lesions depicted in this Image in Clinical Medicine appear to be the typical symmetric papules and plaques with collarette scales (i.e., Biett collarettes) seen on the palms and soles in secondary syphilis. The lesions shown appear to be classic and pathognomonic for secondary syphilis.

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THE AUTHORS REPLY: We agree with Lombardo that the term “keratoderma blennorrhagicum” is often used in conjunction with Reiter’s syndrome. However, syphilis can mimic a number of conditions, and as Lombardo suggests, the lesions look similar to keratoderma. We wanted to make the point that when someone presents with such a rash on the soles, the differential diagnosis should include secondary syphilis.

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