Correspondence

EFFECT OF ATORVASTATIN IN ELDERLY PATIENTS WITH A RECENT STROKE OR TRANSIENT ISCHEMIC ATTACK

To the Editor:

> Hello, grandpa. How's your wife?
> Compared with whom?
>
> —Ancient Vaudeville joke

Before foxy grandpa spends $1,300 per year for atorvastatin pills to prevent the disability of a second stroke—which he fears most—he needs more comparative numbers to set into a rational annual register.[1]

The original study concluded that "the reduction in the risk of nonfatal stroke was consistent with the treatment effect, but not significant."[2] That stroke is a "coronary heart disease risk equivalent" is both statistically correct and common sense. The actual annual second stroke risk for elderly control patients (median age 72.5 years) was 3.3%, vs those receiving atorvastatin (median age 72.3 years), 2.9%, which is a difference of 0.4%/year. The annual risk of not having a stroke and not taking this drug is 96.7%. A fifth of the study's elderly patients were 75 years or older.

The National Vital Statistics Life Table, based only on age, indicates the probability of dying during the next 365 days (table). For men aged 72–85, 0.4% annual decreased stroke risk must be compared with their 8-fold to 25-fold larger annual risk of nonsurvival (women have better odds). Twice as many of the treatment group's strokes were hemorrhagic compared with the placebo; they had a larger death rate from all causes and more developed hepatic toxicity. A few developed rhabdomyolysis and some must have had muscular symptoms.

Caveat emptor!

William Landau, St. Louis, MO

Disclosure: The author reports no disclosures.

Table National Vital Statistics Life Table

	Male		Female	
Age, y	Death	Survival	Death	Survival
72	3.2	96.8	2.2	97.8
75	4.2	95.8	2.8	97.2
80	6.7	93.3	4.6	95.4
85	10.2	89.8	7.7	92.3

Values are percentages.

To the Editor: Chaturvedi and coworkers[1] concluded that "the results support the use of atorvastatin in elderly patients with recent stroke or TIA." This conclusion can be questioned when the statistics and the results are reviewed.

According to their study, the primary endpoint (fatal or nonfatal stroke) was reduced by 10% in elderly subjects (hazard ratio 0.90, 0.73 to 1.1 [$p = 0.33$]). Nonsignificant p values were also found for the subgroup analysis of the primary outcome measures. They argue that a test of heterogeneity for a treatment–age interaction was not significant.

From a biometrical point of view, this questionable test does not seem relevant because the primary statistical analysis was not significant. These data should be reanalyzed by other statisticians. The conclusions may have to be modified.

This is not only of medical importance but also of major socioeconomic importance due to the high number of patients over the age of 65 who suffer from stroke. A treatment that is evidently not effective should not be approved or applied.

Michael Strupp, Munich, Germany

Disclosure: The author reports no disclosures.

To the Editor: We read with interest the article by Chaturvedi et al.,[1] who retrospectively analyzed the SPARCL trial data to investigate whether statin therapy reduced future stroke risk in older (65+) patients with recent stroke or TIA. Whereas future stroke risk in young patients significantly differed from matched placebo controls (26% risk reduction), the risk reduction for older patients was not significant (10%, $p = 0.33$). However, a test of heterogeneity showed no significant interaction between age and treatment effect ($p = 0.52$). Thus, the accompanying commentary in that issue states, the authors "correctly conclude that statin benefits are shared equally in the two groups." We feel that this conclusion is not justified.

A priori, there are 4 possible interpretations of the 10% vs 26% age-dependent RRR, including 1) only young patients benefited (following the initial p value results); 2) both young and old patients benefited (10% and 26% are indistinguishable and the 26% "wins"); 3) neither young nor old patients benefited (10% and 26% are indistinguishable and the 10% prevails); or 4) the question remains uncertain. Possibilities 2 and 3 are mutually exclusive, yet nothing compels us to choose 2 over 3, as the authors do, rather than the reverse. This leaves 1 and 4.

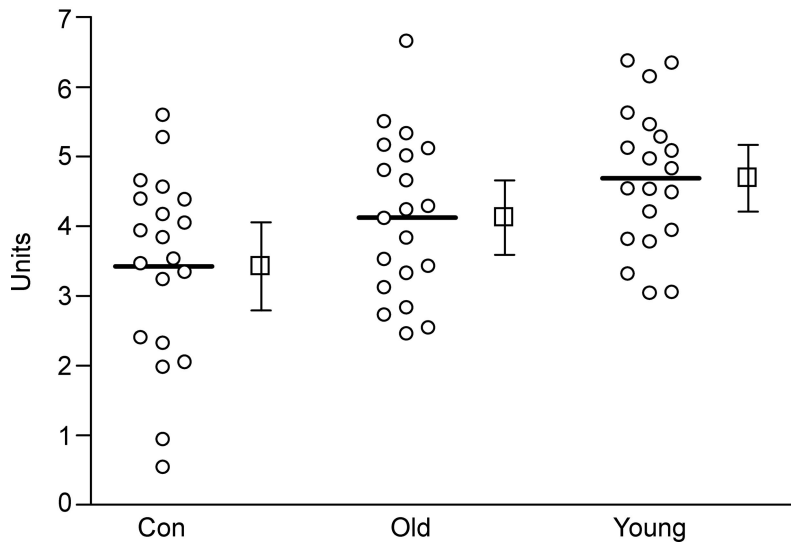
To visualize the dilemma, consider the simulated data (figure), which show 3 groups (n = 20 each) with means of 3, 4, or 5 (arbitrary units of benefit), and variance of 1, for placebo, old, or young patients, respectively. Here, placebo and old are statistically indistinguishable, as are placebo and young, but the young group is different from placebo (as in Chaturvedi et al.). The dilemma is that the middle column (old) is statistically indistinguishable from the other 2 groups, but those groups differ from one another. One can imagine a chain of patient groups, A through Z, each with an incrementally but nonsignificantly larger benefit: if the smallest and largest means, A and Z, are statistically different, it seems unreasonable to conclude that B through Y are all equal to Z, and it seems equally unreasonable to conclude that B through Y are each equal to A.

We find the logic of this article, purporting to show that atorvastatin significantly reduces secondary stroke risk in the elderly, in need of further justification. A plausible conjecture consistent with the data, but not directly addressed by the authors, is that high-dose statin therapy provides stroke risk reduction that gradually diminishes with age.

Matt T. Bianchi, MD, PhD, Brandon Westover, MD, PhD, Boston, MA

Disclosure: The authors report no disclosures.

Figure **Scatterplot and mean, as well as mean ±95% confidence interval (to the right of each scatterplot), for 3 simulated groups, in arbitrary units of "benefit"**



The mean in each group was 3, 4, or 5 units, with a variance of 1 in each case. Standard parametric t test comparisons yielded the following: Con vs Old: $p < 0.09$; Old vs Young: $p < 0.11$; Con vs Young: $p > 0.002$.

Reply from the Authors: We appreciate the thrust of Dr. Landau's comments, but disagree with several of his statements concerning our exploratory analysis. The primary trial was neither designed nor powered to detect a treatment effect in the subgroup of patients older than 65 years. The 95% confidence interval around the hazard ratio in the elderly subgroup overlaps with that of younger subjects, and there was no age-related heterogeneity in the treatment effect.

Although treatment was associated with an increase in hemorrhagic stroke, this was included in the primary endpoint showing benefit. The rates of myalgias, myopathy, and hepatotoxicty were very low and did not differ between elderly and younger subjects. There was no significant difference in all-cause mortality in the older subjects; they tended to have lower rates than the younger group. The absolute risk reduction for any cardiovascular event was 4.1% in the elderly vs 3.0% in the younger group. SPARCL was a randomized trial and is internally valid. The application of vital statistics to this selected population is not appropriate. We stand by the conclusions as reflected in our publication.

We also thank Dr. Strupp and Dr. Bianchi for their comments. As indicated in our response to Dr. Landau, the SPARCL trial was neither designed nor powered to detect subgroup treatment effects. When conducting exploratory subgroup analyses, the nominal subgroup p value can be misleading, and other studies using this type of analysis have been appropriately criticized.[3]

We used the recommended statistical approach: to test for a subgroup interaction based on the study prespecified endpoints.[4] There was no heterogeneity between older and younger subjects for the SPARCL primary or any secondary endpoint. Our analysis was exploratory yet based on the results, it is not appropriate to deny an effective therapy to stroke patients based on their older age.

Seemant Chaturvedi, MD, FAHA, FAAN, Detroit, MI

Disclosure: The study to which this Correspondence refers was sponsored by Pfizer. Dr. Chaturvedi has served as a consultant to Pfizer.

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NEURODEGENERATION ASSOCIATED WITH GENETIC DEFECTS IN PHOSPHOLIPASE A_2

To the Editor: In their article, Gregory et al.[1] describe 2 main pathologic features of infantile neuroaxonal dystrophy and idiopathic neurodegeneration with brain iron accumulation: axonal spheroids and iron deposits. The authors describe these 2 elements as unrelated and induced by the defective phospholipase A2.

However, I believe that the accumulated iron plays a role in spheroid formation. As the authors note, the association of spheroids and iron accumulation appears in another disease, pantothenate kinase-associated neurodegeneration (formerly Hallervorden-Spatz syndrome).[2] Iron-positive macrophages were described in another rare disease, hereditary diffuse leukoencephalopathy with spheroids.[3]

Moreover, the combination of axonal spheroids and iron deposits is seen in non-metabolic disorders, such as superficial siderosis of the CNS. In this disorder, chronic or intermittent spilling of blood into the subarachnoid space and spread of heme by the CSF causes infiltration of iron and ferritin in the cortex associated with abundant axonal spheroids.[4] Spheroids were described in the vicinity of hemosiderin-laden macrophages surrounding arteriovenous malformations, and even in hemorrhagic infarctions.[5] Thus, accumulation of iron alone may induce spheroid formation.

The spheroids of the hereditary diseases may differ from those of superficial siderosis of the CNS. However, the strong association of spheroids and iron in hereditary diseases and acquired disorders suggests a causative relation, and perhaps the toxic effect of iron has a role in spheroid formation.

Menachem Sadeh, Holon, Israel

Disclosure: The author reports no disclosures.

Editor's Note: The authors of the article were offered the opportunity to respond but declined.

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CORRECTION

Association between late-life body mass index and dementia: The Kame Project

In the article "Association between late-life body mass index and dementia: The Kame Project" by T.F. Hughes et al. (*Neurology*® 2009;72:1741–1746), reference 6 (Atti et al.) should not be referenced in the Introduction, page 1741, paragraph 1, sentence 2. All other uses of this reference are correct. The authors regret the error.