

Editors' Note: Friedrich Thinnies proposes an interesting hypothesis for the association between skin cancer and reduced Alzheimer disease risk. Willey critiques the statistical methods in the study by Martínez-Sánchez et al. on statins and stroke severity. However, both parties agree that no definite conclusion can be made before a clinical trial on acute treatment of stroke patients with statins is completed. Martin discusses his experience with trigger factors in migraine and points out to Hougaard et al. that triggers have been studied in the past, contrary to the authors' claim.

—Chafic Karam, MD, and Robert C. Griggs, MD

NONMELANOMA SKIN CANCER IS ASSOCIATED WITH REDUCED ALZHEIMER DISEASE RISK

Friedrich P. Thinnies, Göttingen, Germany: I propose a biologically based hypothesis for the association between skin cancer and reduced Alzheimer disease (AD) risk.¹ Amyloid A β peptides, cut from the amyloid precursor protein of neurons, are assumed to induce brain-wide neuronal apoptosis via opening plasma lemma-standing type 1 voltage-dependent anion channels (VDAC). This process results in AD whenever critical brain regions are affected.^{2–4} Either reaction partner carries one or several GxxxG motifs. Furthermore, data indicate that amyloid A β peptides can be extruded from the brain by ABC transporters at the blood–brain barrier and cancerous transformations accompany changes in the expression level or the functionality of multidrug resistance modulators that then disturb chemotherapy.⁵ However, enhanced extrusion of apoptogenic amyloid A by raised ABC transporter activities of cancer survivors might diminish or even abolish intrabrain apoptotic effect. These findings, along with other data,⁵ may explain why cancer survivors have a lower risk of AD. Finally, the VDAC/amyloid interaction model of AD pathogenesis could explain the reverse relationship of AD and cancer.⁵

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TREATMENT WITH STATINS AND ISCHEMIC STROKE SEVERITY: DOES THE DOSE MATTER?

Joshua Willey, New York: Martínez-Sánchez et al. addressed the issue of nonrandomization of trial participants taking statins before stroke (confounding by indication), using propensity scores.¹ This statistical method may not fully account for prestroke imbalances, which may affect the probability that a patient would be prescribed a statin as an outpatient. For example, older patients with atrial fibrillation (AF) who are likely to have larger strokes may be less likely to be prescribed statins (table 1).¹ Comparing tables 1 and 2, what accounts for the difference in the proportion of patients with AF and those with cardioembolic strokes? What would occur if AF, or cardioembolic vs all others, was included in the models from table 3? In those models, all stroke subtypes are included but with such small numbers that a model fit may be problematic. Until a clinical trial is completed with high doses acutely administered, we caution against high doses being administered to all stroke types. The data support not withholding statins,² but at least one study raised the possibility of no benefit from statins in the acute setting with a trend to worse outcomes.³

Author Response: Patricia Martínez-Sánchez, Blanca Fuentes, Elena Díaz-Domínguez, Marta Martínez-Martínez, Exuperio Díez-Tejedor, Madrid: We thank Dr. Willey for his comments on our

study, where we reported 283 cardioembolic strokes.¹ Of those patients, 27.9% were taking low to moderate doses and 3.2% were taking high doses of statins prior to stroke. The percentage of patients with mild stroke severity (NIH Stroke Scale score less than or equal to 5) was higher in the high-dose statin group, followed by the low- to moderate-dose statin group and the nonstatins group (55.6%, 44.3%, and 34.4%, respectively, $p = 1.164$). After multivariate adjustment, pretreatment with statins was associated with a higher probability of mild stroke severity, reaching statistical significance only in the low- to moderate-dose statin group (odds ratio [OR] 1.812, 95% confidence interval [CI] 1.014–3.239 for the low to moderate doses and OR 3.205, 95% CI 0.804–12.770 for the high doses). We could not perform the propensity score in this group due to the limited sample size. These results suggest that pretreatment with statins is related to lower stroke severity also in larger strokes, which confirms previous experimental⁴ and clinical studies.⁵ An observational study found more extensive collaterals in patients taking statins before stroke.⁶ Whether starting statin therapy in the acute phase of ischemic stroke is associated with better outcome needs to be addressed in future clinical trials.

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PROVOCATION OF MIGRAINE WITH AURA USING NATURAL TRIGGER FACTORS

Paul R. Martin, Brisbane, Australia: It is interesting to see Hougaard et al.¹ use a novel provocation technique to investigate migraine triggers because this is a neglected area of scientific inquiry. However, their suggestion that provocation studies of “natural” triggers have not been carried out previously is misleading. These studies have validated that stress, “visual disturbance,” noise, and hunger are natural triggers.² One provocation study manipulated flicker, glare, and eyestrain and found—contrary to the contention of Hougaard et al.—that these did induce headaches.³ Hougaard et al. concluded that it is not enough for patients to identify triggers; rather, they should challenge themselves with the trigger to confirm its authenticity. Many years ago, I encouraged patients to engage in “behavioral experiments” to clarify the genuine triggers.⁴ The authors suggested that if provocation reveals that the trigger is not a trigger then patients should be advised not to avoid it. Although this seems sensible, we argued that learning to cope with triggers (LCT) is a superior approach to advising avoidance of all triggers.⁵ LCT involves avoiding triggers that are detrimental to health but using graduated exposure with other triggers to desensitize and increase tolerance.

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Treatment with statins and ischemic stroke severity: Does the dose matter?

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