High Dose Atorvastatin after Stroke or Transient Ischemic Attack (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels [SPARCL] Investigators)

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At the time of this trial, statins were known to reduce stroke risk in patients with a history of coronary heart disease and in those with an increased risk of cardiovascular disease; this was mostly related to the effect of statin therapy on lowering one's LDL level. However, no studies had shown an effect of statin therapy on reducing stroke risk among patients with a previous stroke or TIA, regardless of baseline cardiovascular risk. As such, the goal of this study was to determine if high-dose statin therapy (atorvastatin 80 mg) could reduce the risk of a recurrent stroke or TIA, following an index stroke or TIA, in patients without a known history of significant coronary or other cardiovascular disease.

Experimental design and statistics: This was a prospective, randomized, placebo-controlled study. Inclusion criteria included age >18yrs old, a prior ischemic or hemorrhagic stroke occurring 1-6 months before randomization, and mRS $\geq$3, and an LDL of 100 – 190mg/dL. At enrollment, patients had no known history of coronary heart disease. Exclusion criteria included concurrent atrial fibrillation, other cardiac sources of an embolism, or subarachnoid hemorrhage. Patients who were previously on lipid-lowering drugs discontinued these medications 30d before screening. All eligible patients were then randomly assigned to either placebo or atorvastatin 80 mg daily and additionally counseled on appropriate dietary modifications. The primary efficacy outcome was the time to a first fatal or non-fatal stroke, with secondary efficacy outcomes including the following: recurrent stroke or TIA, major coronary event, major cardiovascular event, acute or any coronary event, any revascularization protocol, or any other cardiovascular event. Labs and ECGs were obtained regularly throughout the study protocol at planned follow ups. Statistically, data were analyzed on an intention-to-treat basis, with all patients who underwent randomization included. Log-rank tests were used to compare the time from randomization to a first event in both groups, hazard ratios were calculated, and ARR + NNT values were deduced from Kaplan-Meier curves.

Results: A total of 4731 patients underwent randomization (2365 to atorvastatin, 2366 to placebo); baseline patient characteristics were similar (**Table 1**). Baseline LDL levels were also similar among the two groups, but LDL levels decreased by 53% over 1 month (to a value of 61.4 mg/dL) in the atorvastatin group, with no change in the placebo group. In terms of the primary efficacy outcome, atorvastatin use significantly reduced the composite outcome of any fatal or nonfatal stroke (ARR of 16%, HR: 0.84, p = 0.03, **Table 2 & Fig 2**); of note, the risk of a fatal stroke was significantly reduced with atorvastatin use (HR: 0.57, p = 0.03) but the risk of a non-fatal stroke was only substantially reduced (HR: 0.87, p = 0.11). TIA risk was also significantly reduced with atorvastatin vs. placebo (HR 0.74, p< 0.01), as were the risks of most other secondary outcomes (i.e., virtually all coronary and/or cardiovascular events that were analyzed, **Table 2 & Fig 3**). Notably, post-hoc analyses did show that despite fewer ischemic strokes with atorvastatin treatment, there was an increased risk of a hemorrhagic stroke across the study in the atorvastatin vs. placebo group (adjusted HR of 1.66). Otherwise, there were no group differences in the rates of significant adverse effects, other than persistently elevated AST/ALT levels (though w/o rhabdomyolysis) in the atorvastatin group.

Conclusion: Overall, this study highlighted the benefit of high dose statin therapy for secondary, ischemic stroke prevention following an index stroke or TIA, specifically in patients without another indication for statin therapy. This was largely due to the ability for atorvastatin to lower LDL levels and associated atherosclerotic complications, as both were observed in this study. There was a notable,

increased risk for a recurrent hemorrhagic stroke with atorvastatin, though not entirely surprising given that this outcome had been observed in a prior study (the Heart Protection Study, 2004), using simvastatin 40 mg. The etiology for this association was not clear, though consistent enough to recommend cautious use of statins in patients with a prior hemorrhagic stroke. Otherwise, this data supported the initiation of atorvastatin 80 mg following an ischemic stroke for secondary stroke/TIA prevention (i.e., as in current AHA guidelines). It should be noted, however, that many patients with an index, cardioembolic stroke were likely excluded from this study (based on exclusion criteria), so the use of statins does not entirely pertain to patients with a cardioembolic stroke and no atherosclerotic disease.

Summary created by Elaine Sinclair, D.O.

Additional reading, if interested:

1) Amarenco, P. et. al., **A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke**. NEJM, 2020, 382 (1): 9-19.