There was an increased risk of hemorrhagic stroke with use of a high-dose statin in secondary stroke prevention.

Clinical Problem: *A 74-year-old man is admitted to hospital with ischemic stroke. You are planning on starting atorvastatin given his elevated LDL-cholesterol. You are concerned about his risk of intracerebral haemorrhage.*

Clinical Question:*In patients with stroke, does the use of a high-dose statin increase the risk of intracerebralhemorrhage?*

Search Strategy: Cochrane was searched using the terms "intracerebral hemorrhage" AND "statin", yielding no results.
Pubmed was searched using the terms "intracerebral hemorrhage" AND "statin" with the limits "Meta-Analysis", "English", and "humans". The one article found was not chosen as it was a meta-analysis of case-control studies. The search was expanded; the limit of "Meta-Analysis" was changed to "Randomized Controlled Trial".The SPARCL study, the largest randomized controlled trial and its post-hoc analyses were chosen as they most directly answered the clinical question and were the highest level of available evidence.

Clinical Bottom Lines:

1. In patients with recent ischemic or hemorrhagic stroke, the initiation of high-dose statin is associated with an increased risk of non-fatal intracranial hemorrhage (HR 2.40, 95% CI 1.34 to 4.30), but there was no difference in fatal hemorrhagic stroke.

2. The risk of hemorrhagic stroke was highest in patients with small vessel stroke (lacunar) (HR4.99, 95% CI1.71 to 14.61) and hemorrhagic stroke (HR4.06, 95% CI 0.84 to 19.57).

The Evidence: Prospective, multi-centre, double-blind, randomized, placebo-controlled trial. Patients were randomized to receive atorvastatin 80 mg/day or placebo. The study enrolled 4731 patients, having a median follow-up period of 4.9 years. The aim of the study was to evaluate the effect of lowering cholesterol with a statin on cerebrovascular and cardiovascular endpoints.

Inclusion criteria: Study participants were aged ≥ 18 years with stroke (ischemic or hemorrhagic) or TIA documented in the 1–6 months prior to randomization, low-density lipoprotein cholesterol (LDL-C) level ≥ 2.6 mmol/l and ≤4.9 mmol/l, and functionally independent (Modified Rankin Score of ≤ 3). Exclusion criteria included pregnancy or breast-feeding, a history of CHD; significant peripheral vascular disease (PVD); atrial fibrillation; prosthetic heart valves; clinically significant mitral stenosis; sinus node dysfunction; uncontrolled hypertension, stroke caused by a revascularization procedure or trauma (as qualifying entry event); subarachnoid hemorrhage (as qualifying entry event);hematologic conditions that may cause thrombus formation; endarterectomy within 1 month before randomization; severe renal dysfunction or nephrotic syndrome; and various contraindications to statin therapy.

Outcomes: The primary outcome was the time from randomization to a first nonfatal or fatal stroke. Secondary composite outcomes were stroke or TIA, coronary and cardiovascular events (e.g. major events such as death or nonfatal MI and revascularization procedures).

Data: Entry events of the 4731 participants were 67% ischemic stroke, 31% TIA, 2% hemorrhagic stroke.

Table 1: Occurrence of hemorrhagic stroke [3]

Hemorrhagic stroke type	Atorvastatin Events (N=2365)	Placebo Events (N=2366)	Hazard Ratio (95% CI)	Attributable Risk
Fatal	17 (0.7%)	18 (0.8%)	0.95 (0.49, 1.84)	-0.1%
Non-fatal	38 (1.6%)	15 (0.6%)	2.40 (1.34, 4.30)	1%
Total	55 (2.3%)	33 (1.4%)	1.68 (1.09, 2.59)	0.9%

Table 2: Hemorrhagic stroke by entry event [3]

Entry Event	Atorvastatin, n/N (%)	Placebo, n/N (%)	HR (95% CI)
Large vessel atheroembolic or cardioembolic	8/396 (2.0)	7/401 (1.8)	1.16 (0.42, 3.19)
TIA	12/708 (1.7)	12/752 (1.6)	1.07 (0.48, 2.37)
Small vessel (lacunar)	20/708 (2.8)	4/701 (0.6)	4.99 (1.71, 14.61)
Stroke of unverified type	8/506 (1.6)	8/463 (1.7)	0.91 (0.34, 2.44)
Hemorrhagic stroke	7/45 (15.6)	2/48 (4.2)	4.06 (0.84, 19.57)
All subjects	55/2365 (2.3)	33/2366 (1.4)	1.68 (1.09, 2.59)

Factors shown to be independently associated with the risk of hemorrhagic stroke were determined by Cox multivariable regression and are shown in Table 3.

Table 3: Factors independently associated with hemorrhagic stroke [3]

Factor	Hazard Ratio (95% CI)	P value
Hemorrhagic stroke entry event	5.65 (2.82, 11.30)	<0.001
Male sex	1.79 (1.13, 2.84)	0.01
Atorvastatin treatment	1.68 (1.09, 2.59)	0.02
Age (10y increment)	1.42 (1.16, 1.74)	0.001

Comments:

1. The study was well designed. Few were lost to follow-up (25/4731, or 0.5%). The analysis was on an intention-to-treat basis. However, it is uncertain whether the randomization was concealed.
2. There was no overall heterogeneity between entry event subtypes (p = 0.421 for

heterogeneity).

3. The SPARCL study excluded patients with cardiogenic embolism or coronary heart disease.
4. A large number of participants, 969 (20%), had an entry event (stroke) of unverified cause.
5. Patients with hemorrhagic stroke as the entry event were a small fraction of study subjects, composing only 2% of the study population (93 patients).
6. Subgroup data came from a post-hoc analysis. No correction was made for multiple comparisons.

References:

1. Amarenco P, Bogousslavsky J, Callahan AS, et al. Design and baseline characteristics of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study. Cerebrovasc Dis 2003;16: 389-95.

2. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549–559.

3. Goldstein LB, Amarenco P, Szarek M, et al. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology 2008;70;2364

4. Amerenco P, Benavente O, Goldstein LB, Callahan A, Sillesen H, Hennerici MG, Gilbert S, Rudolph AE, Simunovic L, Zivin JA, Welch MA. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes. Stroke 2009;40:1405-1409.

Key Words:hemorrhagic stroke, intracranial hemorrhage, high-dose statin, atorvastatin

Appraiser: Lauren Mai and the UWO Evidence Based Neurology Group

Date Appraised: November 15, 2011

Copyright 2002-2011
Evidence Based Neurology Group
University of Western Ontario