

An Overview of SPARCL – Stroke Prevention by Aggressive Reduction in Cholesterol Levels

SPARCL Trial Overview ¹

A multi-center prospective, randomized, doubled blinded, placebo-controlled trial evaluating the efficacy of high dose atorvastatin for the prevention of stroke recurrence (fatal and non fatal) after a recent stroke or transient ischemic attack (TIA) in patients with “normal” cholesterol levels (LDL: 2.6-4.9 mmol/L) and NO known history of coronary heart disease. (intention to treat analysis; all patients enrolled were included in final analysis)

- ♦ two treatment arms: ♦ **atorvastatin 80mg daily** (n=2365) ♦ **placebo** (n=2366)
- ♦ **4,731 patients** were followed for **4.9 years** (4.0-6.6yrs) with the following characteristics:
 - males^{~60%} & females with previous stroke/TIA^{~30%} (ischemic^{~66%}, hemorrhagic^{~2%}, embolic, lacunar & cryptogenic within 1-6 months of enrollment),
 - average time since entry event: 87.1 days (atorvastatin), 84.3 days (placebo)^{*significant difference}
 - **age**: mean ~63 years **Baseline LDL** mean: **3.4 mmol/l** (Range: 2.6-4.9mmol/l); **BMI**: 27.5 kg/m² **BP**: 139/82 mm Hg
 - smokers^{~19%}, former smokers^{~40%}, **hypertension**^{~62%}, history of **diabetes**^{~17%}; Framingham not calculated, estimated^{10%}

Table 1: SPARCL Results

Endpoints	Atorvastatin % (n=2365)	Placebo % (n=2366)	ARR %	RRR %	NNT/ 4.9 yrs	p value *unadjusted
1^o Nonfatal or fatal stroke *only first event for each patient counted	11.2 (265 events)	13.1 (311 events)	1.9	15	53	0.05
2^o TIA	6.5	8.8	2.3	26	43	0.004
2^o Major Coronary Event**	3.4	5.1	1.7	33	59	0.006
2^o Major Cardiovascular Event** & Stroke	14.1	17.2	3.1	18	32	0.005
2^o Death (any cause)	9.1	8.9	0.2	2	NS	0.77

* unadjusted p values calculated by the log-rank test, adjusted treatment hazards ratios, 95% CIs, and p values available in original study ** includes death from cardiac causes, nonfatal MI, or resuscitation after cardiac arrest **1^o**=primary outcome **2^o**=secondary outcome **ARR**=absolute risk reduction **CV**=cardiovascular **NNT**=number needed to treat to benefit 1 patient **NS**=not statistically significant **pl**=placebo **RRR**=relative risk reduction **TIA**=transient ischemic attack

Of Note:

- ♦ Concomitant meds at baseline: ACE-I^(~28%), ASA or other antiplatelet drugs(excluding heparin,^(~87%)), β-blocker^(~18%), dihydropyridine derivative^(15%), warfarin^(~6%), ARB^(~4%), prior statin use^{~2.5%}, unknown thiazide diuretic use
- ♦ To account for significant heterogeneity of patients at baseline, treatment hazard ratios, 95% CI and p-values were adjusted for geographic region, entry event (stroke or TIA) time since entry event, sex, and age at baseline.
- ♦ Open label statin use reported in 11.4% of atorvastatin arm and in **25.4%** of placebo arm
- ♦ **LDL** mean levels during treatment:**1.9 vs 3.3mmol/l**^{atorv vs pl}; HDL mean: 1.32 vs 1.3mmol/l^{atorv vs pl}; TC mean: 3.8 vs 5.4 mmol/l^{atorv vs pl}; TG mean: 1.3 vs 1.6 mmol/l^{atorv vs pl}
- ♦ **SAFETY:**
 - ALT/AST elevations >3 x ULN in 51 pts^{2.2%} in the **atorvastatin** arm & 11 pts^{0.5%} in the placebo arm, p<0.001 **NNH=59**, no liver failure
 - **Creatine kinase** elevations >10 x ULN occurred in 2 patients (0.1%) in the **atorvastatin** arm
 - NS↑ of **Non CV death** 138^{5.8%} **atorvastatin** vs 113^{4.8%} placebo p=.102; NS↓ of **CV death** 78^{3.3%} in **atorvastatin** arm vs 98^{4.1%} p=0.11
 - **Permanently discontinued study med**: 17.5% in **atorvastatin** arm, 14.5% placebo arm
 - **Adverse Events**: (atorvastatin/placebo): myopathy^{0.3/0.3%}, rhabdomyolysis^{0.1/0.1%}, myalgia^{5.5/6.0%}, accidental injury^{20.6/18.9%}, hypertension^{16.7/18.7%}, pain^{15.1/16.4%}, diarrhea^{10.1/7.9%}, back pain^{11.2/10.2%}
 - ↑ **Hemorrhagic stroke**: 2.3 vs 1.4%^{55 atorvastatin vs 33 pl cases} **NNH:112** (also ↑d in those with previous CV hx^{HPS 1.3 vs 0.7%^{simvastatin 40mg vs pl}})³

What we knew and what these results add to that knowledge:

- ♦ A meta analysis of previous RCTs on the effects of statins on **primary** stroke prevention suggest that statins reduce the incidence of stroke in **hyperlipidemic patients both with and without CHD** (RR:0.75 & 0.77 respectively).²
- ♦ HPS showed statin therapy^{simvastatin 40mg vs placebo} reduced the rate of **primary and/or secondary (fatal or non-fatal) stroke** in patients **with CHD** (4.3%^{Simvastatin} vs 5.7%^{placebo}, **NNT=72**) **regardless of baseline lipid levels**(but **not** those with pre-existing stroke)³
- ♦ **SPARCL**: aggressive lipid therapy (atorvastatin 80mg/d) appears to reduce the overall incidence of secondary ischemic/unclassified strokes and “major cardiovascular events” in patients without known CHD
- ♦ **Magnitude of benefit**: **one less** secondary stroke for every **53 patients (with a recent stroke/TIA)** treated for **4.9 years**. Reduction in TIA^{NNT:43}, Major Coronary Events^{NNT:59} & Major CV events^{NNT:32}, **NO reduction** in overall mortality.
- ♦ **Magnitude of harm**: **one more hemorrhagic stroke** for every **112 patients** treated ^{atorvastatin 80mg} for 4.9 years.
- ♦ **Heads-Up:**
 - 1) Excluded 19.1% (1939) of the initially screened population, including the exclusion of patients with atrial fibrillation and other cardiac sources of embolism therefore may not be able to extrapolate benefit of routine high-dose atorvastatin to ischemic strokes of cardioembolic origin which is generally the cause of 1 in 5 ischemic strokes⁴
 - 2) Significant reduction in incidence of fatal stroke^{p0.04} only, with a non-significant reduction in non-fatal strokes^{p0.14}
 - 3) Unknown whether lower dosages of atorvastatin would have less harm & a similar benefit (atorvastatin 10mg=\$800; 80mg= \$1050 per yr)
 - 4) Overall benefit modest in heterogeneous population
 - 5) Since the number of nonfatal stroke^{247 vs 280} was not different between groups, it would be interesting to see if a difference in stroke severity was present (preliminary data presented by Goldstein at the ANA 131st Meeting suggests ↓ stroke severity)

References:

- 1) Amarencu P, Bogousslavsky J, Callahan A, et al. High-Dose Atorvastatin after Stroke of Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (**SPARCL**). *NEJM* 2006;355(6):549-559. (Amarencu P, on behalf of the SPARCL investigators. Stroke Prevention by Aggressive Reduction in Cholesterol Levels. World Congress of Cardiology 2006: September 3, 2006: Barcelona, Spain.)
- 2) Briel M, Studer M, Glass T, et al. Effects of Statins on Stroke Prevention in Patients with and without Coronary Heart Disease: A Meta-analysis of Randomized Controlled Trials. *Am J Med.* 2004;17:596-606. (Amarencu P, et al. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke*. 2004 Dec;35(12):2902-9. Epub 2004 Oct 28.)
- 3) Heart Protection Study Group. MRC/BHF Heart Protection Study of Cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet*. 2002;360:7-22. (Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004 Mar 6;363(9411): 757-67.)
- 4) Kent DM. Stroke--an equal opportunity for the initiation of statin therapy. *N Engl J Med*. 2006 Aug 10;355(6):613-5.
- 5) Amarencu P, Benavente O, Goldstein LB, et al.; on behalf of the SPARCL Investigators. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes. *Stroke*. 2009 Feb 19. [Epub ahead of print] Atorvastatin 80 mg/d is similarly efficacious in preventing strokes and other cardiovascular events, irrespective of baseline ischemic stroke subtype.