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$^{\sim 60\%}$ & females with previous stroke/TIA$^{\sim 30\%}$ (ischemic$^{\sim 66\%}$, hemorrhagic$^{\sim 2\%}$, embolic, lacunar & cryptogenic within 1-6 months of enrollment),
  average time since entry event: 87.1 days (atorvastatin), 84.3 days (placebo)$^{*\text{significant difference}}$
  - **age**: mean ~63 years **Baseline LDL** mean: **3.4 mmol/l** (Range: 2.6-4.9mmol/l); **BMI**: 27.5 kg/m^2 **BP**: 139/82 mm Hg
  - smokers$^{\sim 19\%}$, former smokers$^{\sim 40\%}$, **hypertension**$^{\sim 62\%}$, history of **diabetes**$^{\sim 17\%}$; 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° 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° TIA	**6.5**	8.8	2.3	26	43	0.004
2° Major Coronary Event**	**3.4**	5.1	1.7	33	59	0.006
2° Major Cardiovascular Event & Stroke**	**14.1**	17.2	3.1	18	32	0.005
2° 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°**=primary outcome **2°**=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$^{(\sim 28\%)}$, ASA or other antiplatelet drugs(excluding heparin,$^{(\sim 87\%)}$), β-blocker$^{(\sim 18\%)}$, dihydropyridine derivative$^{(15\%)}$, warfarin$^{(\sim 6\%)}$, ARB$^{(\sim 4\%)}$, prior statin use$^{\sim 2.5\%}$, 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**$^{\text{atorv vs pl}}$; HDL mean: 1.32 vs 1.3mmol/l$^{\text{atorv vs pl}}$; TC mean: 3.8 vs 5.4 mmol/l$^{\text{atorv vs pl}}$; TG mean: 1.3 vs 1.6 mmol/l$^{\text{atorv vs pl}}$
- **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$^{11.2/10.2\%}$, new-onset diabetes $^{8.7\ /6.1\%}$
  - ↑ **Hemorrhagic stroke:** 2.3 vs 1.4% $^{55\ \text{atorvastatin vs}\ 33\ \text{pl cases}}$ **NNH:112** (also ↑'d in those with previous CV hx $^{\text{HPS}}$ 1.3 vs 0.7%$^{\text{simvastain 40mg vs pl}}$) [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$^{\text{simvastatin 40mg vs placebo}}$ reduced the rate of primary and/or secondary (fatal or non-fatal) stroke in patients with CHD (4.3%$^{\text{Simvastatin}}$ vs 5.7%$^{\text{placebo,}}$ 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$^{\text{NNT:43}}$, Major Coronary Events$^{\text{NNT:59}}$ & Major CV events$^{\text{NNT:32}}$, **NO reduction** in overall mortality.
  Magnitude of harm: **one more hemorrhagic stroke** for every **112 patients** treated $^{\text{atrovastatin 80mg}}$ for 4.9 years.
- *Heads-Up*:
  1) Excluded 29.1% (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 strokes[4]
  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 $^{247\ \text{vs}\ 280}$ 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)

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