



Statins for Stroke Prevention

Vinod M Vijan

Ex-Associate Professor Cardiology, NDMVP Medical College, Nashik; Consultant Cardiologist, Nashik; Ruby Hall Clinic; Breach Candy Hospital, Mumbai; Cumbala Hill Hospital, Mumbai

74

- Stroke is the second leading cause of death worldwide.¹ The relation if any between cholesterol levels and stroke is poorly understood. This is in part, because distinction between ischaemic and haemorrhagic strokes has not been made in relation to cholesterol levels and both have distinct pathophysiologies.²
- In India Community surveys have shown a crude prevalence rate for hemiplegia in range of 200 per 100000 persons nearly 1.5% of all medical and around 20% of neurological cases.³
- India will face an enormous socio-economic burden to rehabilitate stroke survivors because the population is now surviving through peak years (Age 55 - 65) of occurrence of stroke.⁴
- First data on stroke and statins came from LIPID study.⁵ This study was sponsored by a manufacturer of pravastatin, wherein 9014 patients (age range, 31-75) with recent histories of MI or unstable angina and total cholesterol levels of 155 mg/dl to 271 mg/dl were randomised to pravastatin 40mg/d or placebo.

During a mean 6 year follow up, the overall risk factor for stroke was significantly lower among pravastatin recipients than among placebo recipients 3.7% versus 4.4%, a RRR of 19%.

Non-haemorrhagic stroke occurred significantly less often in the pravastatin group 3.4% versus 4.4% a RRR, 23%. The risk of haemorrhagic stroke was similar in both groups. Drug treatment was not associated with higher rate of adverse effects. Baseline

Table 1: Statin therapy and stroke: Results of meta analysis.

References		Sample Size		Stroke (fatal and non-fatal)		Relative reduction in rates, %	95% CI
		Statin	Placebo	Statin	Placebo		
Crouse <i>et al.</i> ¹³	PTT	3908	3900	48	56	15	-0.27-0.42 (<i>P</i> =0.48)
	SPT	5862	5848	134	192	31	0.13-0.45 (<i>P</i> =0.001)
	PSPTT	9770	9748	182	248	27	0.11-0.40 (<i>P</i> =0.01)
Hebert <i>et al.</i> ¹⁴		16,826	11,875	193	261	29	0.59 - 0.88
Ross <i>et al.</i> ³⁴		10,387	10199	74	97	23	0.57 - 1.04 (fatal stroke)
				106	159	33	0.54-0.88 (non-fatal stroke)
Blow <i>et al.</i> ⁶¹		10,314	10,124	181	261	31	0.57-0.83 (<i>p</i> <0.001)

PPT=Primary prevention trials, SPT=Secondary prevention trials; PSPT=Primary and secondary prevention trials.

Table 2: Effect of statin therapy on the primary and secondary prevention of stroke.

	45	WOSCOPS	CARE	LIPID	AFCAPS/TEXCAPS	MIRACL
Type of trial	2°	1°	2°	2°	1°	2°
Statin used	Simva	Prava	Prava	Prava	Lova	Atorva
n	4444	6595	4159	9014	6605	3086
Relative risk reduction (%)	28	11	31	19	N/A	50
<i>P</i> -value	0.033	NS	0.03	0.048	N/A	0.045
LDL-C reduction (%)	35	20	32	25	25	40

2° = secondary, 1° = primary; NS = not significant

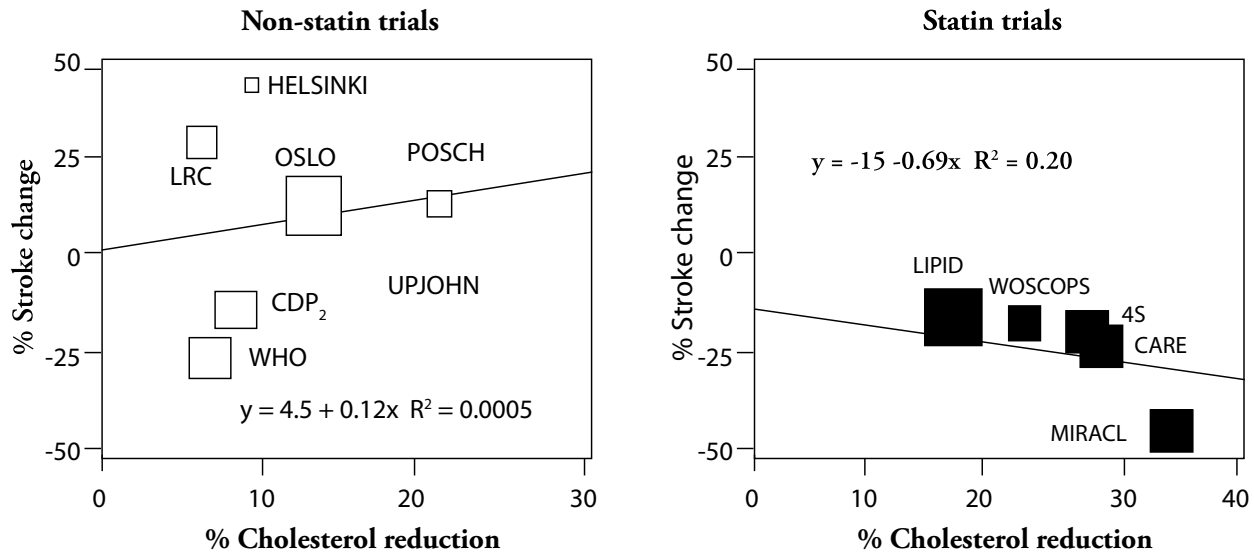


Fig. 1

Conclusion: There is absence of any relationship between cholesterol reduction and all cause strokes in both non-statin and statin trials.

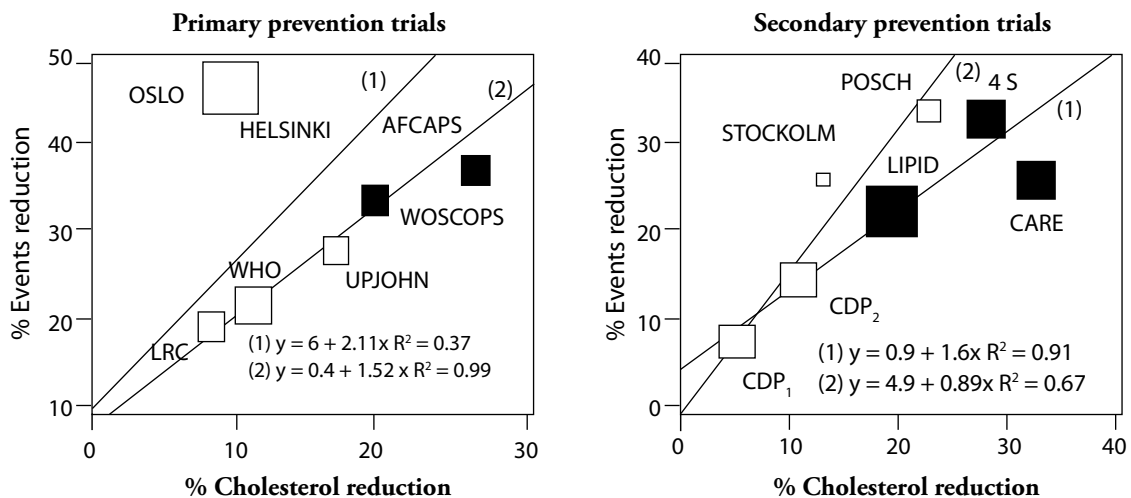


Fig. 2

total and LDL cholesterol levels did not co-relate with overall stroke risk.

- This study is considered as a landmark study as it came in background of several epidemiological studies which had concluded that there is no relation between total cholesterol levels and risk of stroke⁶ and in some an association between low cholesterol levels and risk of haemorrhagic stroke. This conclusion had come from the multiple risk factor intervention trial which although found a positive, continuous relation between cholesterol levels and risk of ischemic stroke, the risk of intracerebral hemorrhage was greater at low levels of cholesterol than at high levels, and this risk was associated with hypertension.⁷ This probably could be a kin to high incidence of haemorrhagic stroke in uncontrolled hypertensive patients on anticoagulants or antiplatelets and statins are known to have antiplatelet effects.

Author's opinion

- Another meta analysis of incidence of stroke in Asian population showed a positive relation between increasing cholesterol levels and non-haemorrhagic stroke.⁸
- On other hand trials which lowered cholesterol by 6-23% by non-statin mechanisms like diet, clofibrate, niacin, colestipol, cholestyramine, gemfibrozil or partial ileal bypass surgery showed no reduction in rate of stroke with respect placebo or no treatment.⁹
- There have been many trials which have shown^{5,10,11,12} that statins have reduced stroke rate by 25-30%. These were limited by failure to classify the type of stroke and small number of strokes (reducing the precision of estimates). Likewise the possible reason for earlier studies to show lack of benefit of statins in stroke could be lower absolute rate of stroke than of coronary events, divergent causes of stroke, relatively young age of patients in those studies. Most had excluded patients over 70 years of age in those studies, a subgroup which forms

15% population and a small overall reduction in cholesterol levels 10-11% as compared to 18% in LIPID study.¹³

- Post analysis of Scandinavian Simvastatin survival study. Simvastatin Vs Placebo^{12,13}
 - Lower incidence of stroke and TIA (28% RR, 3.4% Vs 4.6%) over 5.4yrs in patients with CAD.
 - Incidence of stroke alone was non-significantly lower (RRR 22%).
 - Use of aspirin was low (37%).
- Pre-specified analysis of cholesterol and recurrent events (CARE) study.
 - Pravastatin reduced incidence of stroke by 32% over 5 years Vs Placebo (2.6 Vs 3.8)
 - Use of aspirin was 83%.¹²
 - [Atheroma of carotid arteries and aortic arch is a potent independent risk factor for stroke.
 - Lipid lowering therapy has been shown to reduce progression of carotid intimal thickening.^{16,17}
 - A 29% reduction in late of myocardial infarction and hence with it's complication like LV mural thrombosis, heart failure) could contribute in lowering cardioembolic stroke.⁶

RESULTS OF META ANALYSIS OF SEVERAL MEGATRIALS

Secondary Prevention trials

Statins lower stroke by 24-32%^{13,16}

Primary Prevention Trials

Non-significantly lower rate 15-20%^{13,16}

Linear regression analysis between percentage reduction of cholesterol in all causes of strokes in both statin and non-statin trials.

However percentage of cholesterol reduction both by statin and non-statin mechanism in primary and secondary trials do show a reduction in CV events.

CONCLUSION

Risk of stroke is reduced with use of statins.¹⁸

- SPARCL study.¹⁸

(Stroke Prevention by Aggressive reduction in cholesterol levels).

First study primarily designed to evaluate prospectively effect of statin on secondary stroke prevention using atorvastatin 80 mg.

End-points are primary cerebrovascular (primary) and cardiovascular (secondary) events in patients with TIA/CVA but no CHD. Results are expected in late 2002.
- (There is evidence that statins protect form ischemic Stroke. The effects of statins which are cholesterol independent "Pleiotropic" effects are clinically relevant.¹⁹ This is probably

linked to reduction in isoprenoid intermediates in the mevalonate pathway and exert their neuroprotection by:

1. Nitric oxide bioavailability (Improves endothelial function, plaque stability).
2. Anti-inflammatory effects.
3. Anti-thrombotic effects.

Future

- Extend benefit of statins for total vascular protection.
- Recognition of benefits in coronary and stroke prevention would lead to more wide spread use.
- Discussion of stroke prevention in cardiac patients may reduce non-compliance, a major impediment to clinical implementation.

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