THERAPEUTICS INITIATIVE
Evidence Based Drug Therapy

Do Statins have a Role in Primary Prevention?

Two important questions regarding statin therapy are:

- **What is the overall health impact when statins are prescribed for primary prevention?**
- Should the dose of statin be titrated to achieve target lipid levels?

Three new randomized controlled trials[1-3], which help answer the first question and one trial providing insight into the second question have been published since our last Letter on lipid lowering therapy (#42). This Letter addresses the first question and the next Letter (#49) will address the second.

Estimating the overall health impact of statins in primary prevention requires balancing possible benefits and possible harms. In this Letter benefit is estimated by combining two cardiovascular serious adverse events known to be reduced by statins in secondary prevention trials: total myocardial infarction (fatal and non-fatal)[5] and total stroke (fatal and non-fatal).[6] The balance between benefit and harm (overall health impact) is estimated by total mortality and total serious adverse events. **Serious adverse events include any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of hospitalization, or results in persistent or significant disability.**

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)[1]

PROSPER studied the effect of pravastatin compared to placebo in two older populations of patients: 56% primary prevention (no past or symptomatic cardiovascular disease) and 44% secondary prevention (past or symptomatic cardiovascular disease) (Table 1). Pravastatin did not reduce total myocardial infarction or total stroke in the primary prevention population, RR 0.94 [0.78 – 1.14], but did so in the secondary prevention population, RR 0.80 [0.68 – 0.94], ARR 4.3%, NNT 23 for 3.2 years. Measures of overall health impact in the combined populations, total mortality and total serious adverse events, were unchanged by pravastatin as compared to placebo, RR 0.98 [0.84 – 1.14] and 1.01 [0.96 – 1.06], respectively.

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)[2]

ALLHAT-LLT was designed to determine whether pravastatin compared with usual care reduces all-cause mortality in older, moderately hypercholesterolemic, hypertensive patients with at least 1 additional coronary heart disease risk factor. The published data is for the whole population, 86% of which was primary prevention. Pravastatin did not reduce total myocardial infarction and total stroke, RR 0.91 [0.82 – 1.01]. Pravastatin also did not reduce total mortality, RR 0.99 [0.89 – 1.09]. Total serious adverse events were not reported.

Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA)[3]

ASCOT-LLA was designed to assess the benefits of atorvastatin versus placebo in hypertensive patients with average or lower-than-average cholesterol concentrations and at least 3 other cardiovascular risk factors. The published data is for the whole population, 82% of which was primary prevention. The trial was originally planned for 5 years, but was stopped after a median follow-up of 3.3 years because of a significant reduction in cardiac events. Atorvastatin reduced total myocardial infarction and total stroke, RR 0.82 [0.70 – 0.96], ARR 1.2%, NNT 83. Total mortality was not significantly reduced, RR 0.87 [0.71 – 1.05]. The trial report stated that total serious adverse events "did not differ between patients assigned atorvastatin or placebo", but the actual numbers of serious adverse events were not given.

What is the overall health impact when statins are prescribed for primary prevention?

To attempt to answer this question we combined the data from the 5 mostly primary prevention trials, the 3 above plus 2 published earlier[7,8] (Tables 1&2). Note that these calculations reflect a population that

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Table 1: Characteristics of the 5 major statin primary prevention trials.

Trial	Drug Name	Trade Name	Dose mg/day	N	Average age (yr)	%male	%Primary Prevention	Baseline x̄ Tchol. (mmol/L)	Δx̄ Tchol*
PROSPER[1]	Pravastatin	Pravachol®, generic	40	5,804	75	48	56	5.7	-19
ALLHAT-LLT[2]	Pravastatin	Pravachol®, generic	40	10,355	66	51	86	5.8	-11
ASCOT-LLA[3]	Atorvastatin	Lipitor®	10	10,305	63	81	82	5.5	-24
AFCAPS[7]	Lovastatin	Mevacor®, generic	20 - 40	6,605	58	85	100	5.7	-19
WOSCOP[8]	Pravastatin	Pravachol®, generic	40	6,595	55	100	92	7.0	-20

* % reduction in the statin group minus the control group after 1 to 2 years of therapy.   N = total number of patients in trial.   x̄ = mean.   Δ = change.

is 84% primary prevention and 16% secondary prevention. In the pooled data the statins reduced the cardiovascular measures, total myocardial infarction and total stroke, by 1.4% as compared to control. This value indicates that 71 mostly primary prevention patients would have to be treated for 3 to 5 years to prevent one such event. This can be compared with the same pooled outcome in 4 large secondary prevention statin trials, ARR 4.8%, NNT 21 for 5 years. (Letter #42, HPS[4])

In the 2 trials where serious adverse events are reported, the 1.8% absolute reduction in myocardial infarction and stroke should be reflected by a similar absolute reduction in total serious adverse events; myocardial infarction and stroke are, by definition, serious adverse events. However, this is not the case; serious adverse events are similar in the statin group, 44.2%, and the control group, 43.9% (Table 2). This is consistent with the possibility that unrecognized seri-

ous adverse events are increased by statin therapy and that the magnitude of the increase is similar to the magnitude of the reduction in cardiovascular serious adverse events in these populations. This hypothesis needs to be tested by analysis of total serious adverse event data in both past and future statin trials. Serious adverse event data is available to trial authors, drug companies and drug regulators. The other measure of overall impact, total mortality, is available in all 5 trials and is not reduced by statin therapy (Table 2).

Conclusions:
• If cardiovascular serious adverse events are viewed in isolation, 71 primary prevention patients with cardiovascular risk factors have to be treated with a statin for 3 to 5 years to prevent one myocardial infarction or stroke.
• This cardiovascular benefit is not reflected in 2 measures of overall health impact, total mortality and total serious adverse events. **Therefore, statins have not been shown to provide an overall health benefit in primary prevention trials.**

Table 2: Meta-analysis of major outcomes from the 5 statin primary prevention trials.

Outcome	Statin %		Control %		RR [95% CI]		ARR%		NNT (3 – 5 yr)	
	5 trials	2 trials*	5 trials	2 trials*	5 trials	2 trials*	5 trials	2 trials*	5 trials	2 trials*
Total mortality	6.6	6.1	6.9	6.2	0.95 [0.88 – 1.02]	0.99 [0.87 – 1.14]				
Total MI and stroke	7.3	8.0	8.7	9.8	0.84 [0.78 – 0.90]	0.82 [0.73 – 0.92]	1.4	1.8	71	56
Total SAEs*		44.2		43.9		1.01 [0.97 – 1.05]				

*AFCAPS[7] and PROSPER[1].   MI = Myocardial Infarction.   SAEs = Serious Adverse Events.

RR = Relative Risk. CI = Confidence Interval. ARR = Absolute Risk Reduction.
NNT = Number Needed to Treat to prevent one event.

References:
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