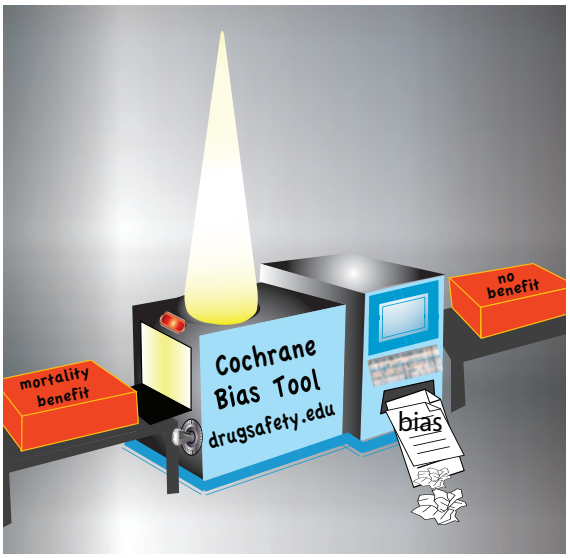
THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Do statins have a role in primary prevention? An update.



Therapeutics Letter #48 (April-June 2003)[1] concluded that "statins have not been shown to provide an overall health benefit in primary prevention trials" based on the 5 RCTs[8-12] available at that time. More RCTs are now available and 5 systematic reviews[2-6] designed to answer this question have been published since 2003. Unfortunately, these reviews do not answer the question "Do the benefits of statins outweigh the harms in people without proven occlusive vascular disease?" This question is critically important to patients, physicians and health care resource utilization.

The Cochrane Collaboration is regarded as the gold standard of systematic reviews. One of its guiding principles is avoiding unnecessary duplication: any independent reviewer following the proper methodology would include the same trials, extract the same data and come to the same interpretation and conclusions. The review is then updated as new trials are published.

The 5 published systematic reviews[2-6] (none of which are Cochrane reviews) vary in the RCTs included, summary effect estimates, conclusions and declared conflicts of interest of the authors (**Table 1**).

Two of these reviews report a decrease in total mortality while 3, including the latest, conclude that mortality is not decreased by statins in this setting.

What is the explanation for the different relative risk estimates? In part, it is due to the timing of the review and the trials that were available for inclusion. The 2006 review[2] did not have access to 3 RCTs[17-19]. The 2007 review[3] did not have access to 2 RCTs[18,19]. The 2008 review[4] did not include 2 RCTs[13,19] and included 10 RCTs[20-29] not included in any of the other reviews. The 2009 and 2010 reviews[5,6] had access to the same RCTs and had very small differences in the RCTs included (**Table 1**). The reason for the variation in the overall mortality estimate between the 2009 and 2010 reviews is that the 2010 review requested and obtained additional details from authors, allowing exclusion of 3659 secondary prevention patients from 4 large RCTs[8,10,11,12].

Table 1. Published systematic reviews

Year	Number of RCTs [ref]	Total mortality RR[95%CI]	Total CHD RR[95%CI]	Conclusions	Declared conflict of interest
2006[2]	7 [8-14]	0.92 [0.84-1.01]	0.71 [0.60-0.83]	Mortality not decreased	4/4 authors no conflicts
2007[3]	8 [8-14, 17]	0.95 [0.89-1.01]	0.77 [0.71-0.83]	Mortality not decreased	1 author none 1 author consultant in litigation against Pfizer
2008[4]	20 [8-12, 14-18, 20-29]	0.93 [0.87-0.99]	0.77 [0.63-0.95]	Mortality significantly decreased	6/6 authors no declaration
2009[5]	10 [8-14, 17-19]	0.88 [0.81-0.96]	0.70 [0.61-0.81]	Mortality significantly decreased	6/12 authors financial conflict
2010[6]	11 [8-12, 14-19]	0.91* [0.83-1.01]	NR	Mortality not decreased	5/7 authors financial conflict

NR - Not reported * random effects model

Why is a new systematic review necessary?

The differences in the interpretation and conclusions of these non-Cochrane reviews are confusing for clinicians. They can be resolved by using Cochrane methodology, including the Cochrane Risk of Bias Tool. Therefore we performed a new systematic review starting with the 22 RCTs included in at least one of these 5 systematic reviews. We excluded 10 of the RCTs[20-29] included in the 2008 review because the population studied was largely or entirely people with occlusive vascular disease at baseline. We included the remaining 12 RCTs[8-19], which provided data for at least one of 3 outcomes that we judged least subject to bias and most meaningful to patients: total all-cause mortality, total people with at least one serious adverse event (SAE) and total people with at least one major coronary heart disease (CHD) serious adverse event. All-cause mortality is an important outcome, for which we used the more accurate data from the 2010 review. Total SAEs capture overall mortality and all serious morbidity. Major CHD (non-fatal MI and death from coronary heart disease) is the outcome specifically reduced by statins, and less subject to bias than other cardiovascular outcomes such as revascularizations and strokes.

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Results. All 12 RCTs report major CHD data, 11 report mortality data and 6 report SAE data. Our meta-analysis demonstrates that the reduction in mortality and major CHD, both SAE outcomes, is not reflected in a reduction in total SAEs (**Table 2**). The results are similar if they are limited to the 6 RCTs [8,9,11,14,16,19] that reported SAEs: mortality RR 0.90 [0.79-0.98], ARR 0.4%; Major CHD RR 0.70 [0.62-0.79], ARR 1.0%.

Table 2. Statins for primary prevention meta-analysis

Mortality			Major CHD			Total SAEs		
# RCTs	RR* [95%CI]	ARR %	# RCTs	RR* [95%CI]	ARR %	# RCTs	RR* [95%CI]	ARR %
11	0.93 [0.86-1.00]	0.3	12	0.74 [0.68-0.80]	1.0	6	0.99 [0.96-1.03]	nil
Sensitivity analysis removing 4 RCTs with high risk of bias								
7	0.99 [0.90-1.08]	nil	8	0.79 [0.72-0.86]	1.3	4	1.00 [0.96-1.05]	nil

*See forest plots in the online version: http://ti.ubc.ca/letter77-appendix

However, getting accurate data entered and analysed is insufficient on its own. Cochrane reviews require assessing the risk of bias for each included RCT using the Risk of Bias Tool. Using this tool we found some risk of bias for each of the 12 included RCTs.

Loss of blinding to treatment allocation probably occurred in all 12 RCTs, because statins predictably lower LDL cholesterol and the physicians managing the patients knew the lipid parameters. This loss of blinding likely biased clinical decisions regarding revascularization procedures and how outcomes were categorized (e.g. transient ischemic attack or reversible ischemic neurological deficit). Fewer revascularization procedures in the statin group as a result of loss of blinding would result in fewer complications secondary to the procedures, e.g. myocardial infarctions.

Other risks of bias affected only some RCTs. Of highest risk are the biases due to stopping RCTs early for benefit, affecting 3 RCTs[12,14,19], and incomplete outcome reporting bias (not an intention to treat analysis), affecting 1 RCT[18]. A recent research study demonstrated that the magnitude of the bias effect from stopping RCTs early for benefit is surprisingly large and robust, RR 0.71 [0.66-0.77].[7] Testing the effect of this bias estimate on the early terminated JUPITER trial changes the RR for major CHD from 0.54 to 0.76 and completely negates the mortality benefit.

In order to test the effect of the bias from these 4 RCTs we removed them; analysis of the remaining 7 RCTs (Table 2, second row) shows no reduction in mortality. This suggests that the claimed mortality benefit with statins for primary prevention is more likely due to bias than being a true effect. Removing the 4 potentially biased trials also diminished the magnitude of the major CHD relative risk reduction from 26% to 21%.

How can CHD SAEs decrease, but not total SAEs?

All CHD events are SAEs and are counted in both categories. Therefore a reduction in major CHD SAEs should be reflected in a reduction in total SAEs. The fact that it is not suggests that other SAEs are increased by statins negating the reduction in CHD SAEs in this population. A limitation of our analysis is that we could not get total SAE data from all the included RCTs. However, we are confident that the data from the 6 missing RCTs would not change the results, because they represent only 41.2% of the total population and include ALLHAT-LLT[10], where one would not expect a reduction in total SAEs; in that trial there was no effect on mortality or cardiovascular SAEs.

Conclusions

• Systematic reviews and meta-analyses are challenging and require much more than locating RCTs and plugging in the numbers.

• The claimed mortality benefit of statins for primary prevention is more likely a measure of bias than a real effect.

• The reduction in major CHD serious adverse events with statins as compared to placebo is not reflected in a reduction in total serious adverse events.

• Statins do not have a proven net health benefit in primary prevention populations and thus when used in that setting do not represent good use of scarce health care resources.

References

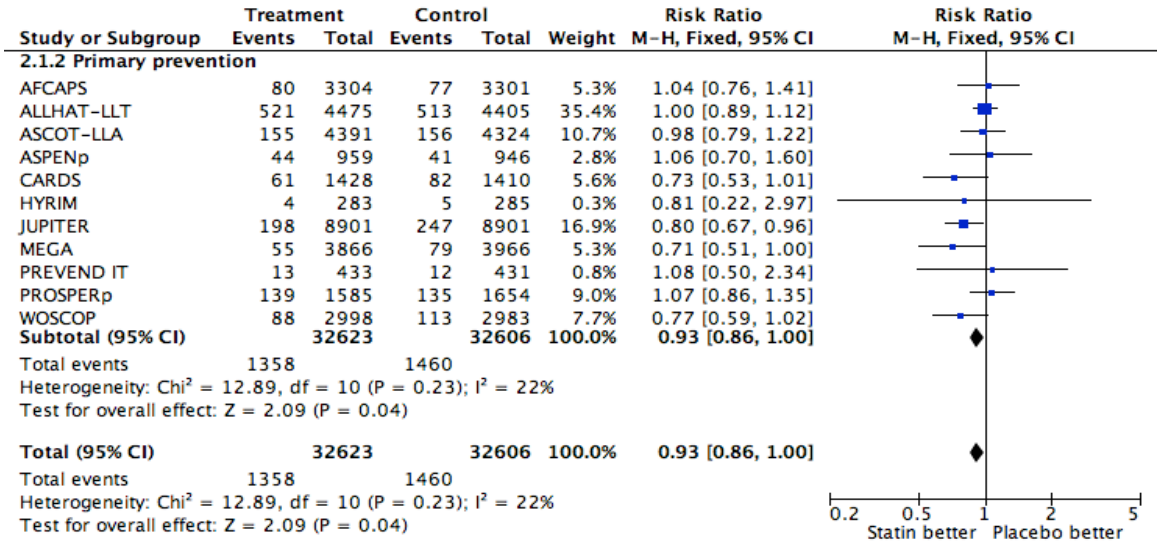
1. Therapeutics Initiative. *Do statins have a role in primary prevention?* Therapeutics Letter. Apr-Jun 2003; 48:1-2. http://www.ti.ubc.ca/pages/letter48
2. Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. *Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials*. Arch Intern Med. 2006;166(21):2307-2313.
3. Abramson J, Wright JM. *Are lipid lowering guidelines evidence-based?* Lancet. 2007;369(9557):168-9.
4. Mills EJ, Rachlis B, Wu P, et al. *Primary prevention of cardiovascular mortality and events with statin treatments*. J Am Coll Cardiol. 2008;52(22):1769-1781.
5. Brugts JJ, Yetgin T, Hoeks SE, et al. *The benefits of statins in people without established cardio-vascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials*. BMJ. 2009;338:b2376. doi:10.1136/bmj.b2376
6. Ray KK, Sreenivasha RKS, Sebhat E, et al. *Statins and all-cause mortality in high-risk primary prevention. A meta-analysis of 11 randomized controlled trials involving 65,229 participants*. Arch Intern Med. 2010;170(12):1024-1031.
7. Bassler D, Briel M, Montori VM, et al. *Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis*. JAMA. 2010;303(12):1180-87.

For the complete list of references, including citations 8-29, go to: http://ti.ubc.ca/letter77#1

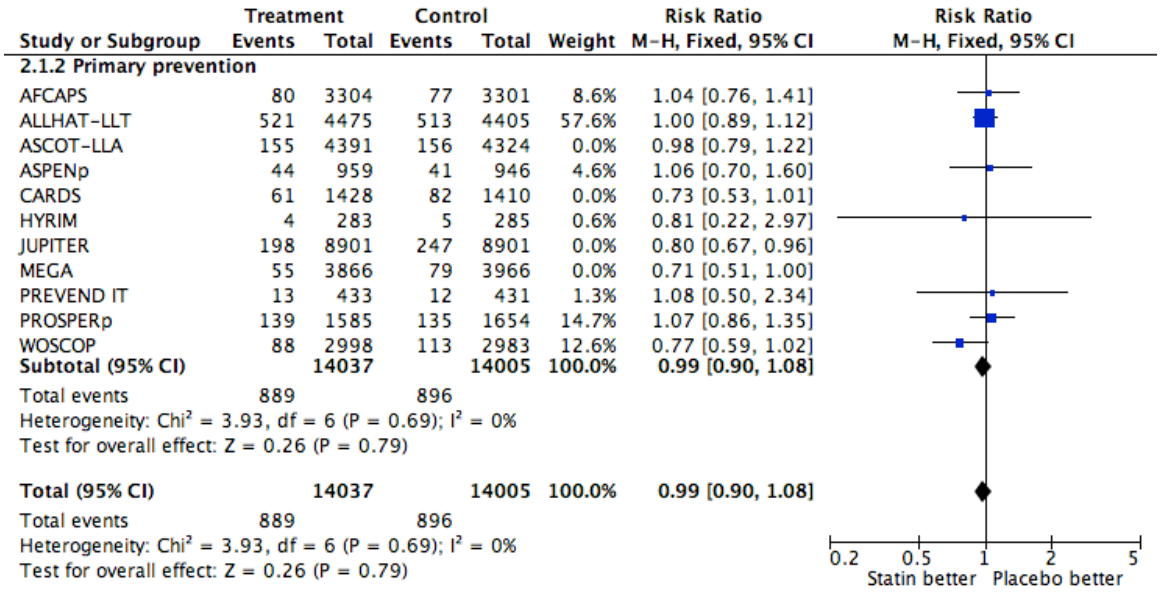
The draft of this Therapeutics Letter was submitted for review to 45 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

Appendix – Forest Plots

1 Outcome. Total Mortality

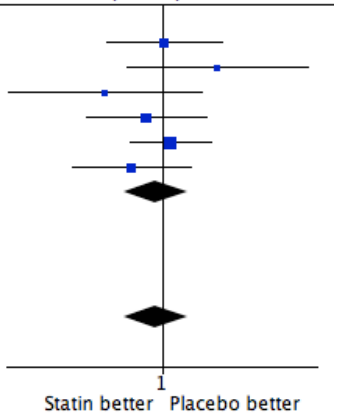


1.1 Outcome. Total mortality [minus 4 biased RCTs]



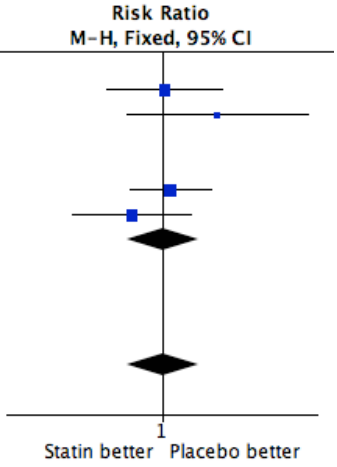
2 Outcome. Serious adverse events.

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.2 Primary prevention						
AFCAPS	1131	3304	1126	3301	18.5%	1.00 [0.94, 1.07]
ASPENp	457	1211	424	1199	7.0%	1.07 [0.96, 1.19]
CARDS	414	1428	437	1410	7.2%	0.94 [0.84, 1.05]
JUPITER	1352	8901	1377	8901	22.6%	0.98 [0.92, 1.05]
PROSPERp	1608	2891	1604	2913	26.3%	1.01 [0.96, 1.06]
WOSCOP	1080	3302	1116	3293	18.4%	0.97 [0.90, 1.03]
Subtotal (99% CI)		**21037**		**21017**	**100.0%**	**0.99 [0.96, 1.03]**
Total events	6042		6084			
Heterogeneity: $Chi^2 = 4.28$, df = 5 (P = 0.51); $I^2 = 0\%$						
Test for overall effect: Z = 0.49 (P = 0.62)						
Total (99% CI)		**21037**		**21017**	**100.0%**	**0.99 [0.96, 1.03]**
Total events	6042		6084			
Heterogeneity: $Chi^2 = 4.28$, df = 5 (P = 0.51); $I^2 = 0\%$						
Test for overall effect: Z = 0.49 (P = 0.62)						

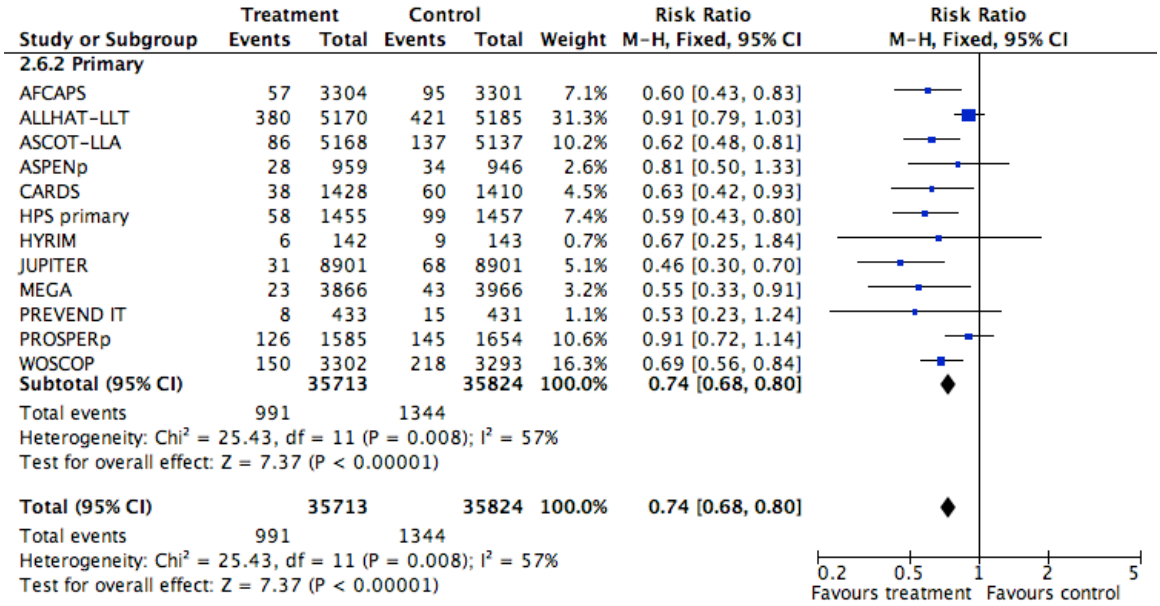


2.1 Outcome. Serious adverse events [minus 2 biased RCTs]

Study or Subgroup	Statin better Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.2 Primary prevention						
AFCAPS	1131	3304	1126	3301	26.4%	1.00 [0.94, 1.07]
ASPENp	457	1211	424	1199	10.0%	1.07 [0.96, 1.19]
CARDS	414	1428	437	1410	0.0%	0.94 [0.84, 1.05]
JUPITER	1352	8901	1377	8901	0.0%	0.98 [0.92, 1.05]
PROSPERp	1608	2891	1604	2913	37.4%	1.01 [0.96, 1.06]
WOSCOP	1080	3302	1116	3293	26.2%	0.97 [0.90, 1.03]
Subtotal (99% CI)		**10708**		**10706**	**100.0%**	**1.00 [0.96, 1.05]**
Total events	4276		4270			
Heterogeneity: $Chi^2 = 2.65$, df = 3 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 0.14 (P = 0.89)						
Total (99% CI)		**10708**		**10706**	**100.0%**	**1.00 [0.96, 1.05]**
Total events	4276		4270			
Heterogeneity: $Chi^2 = 2.65$, df = 3 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 0.14 (P = 0.89)						



3 Outcome. Total coronary heart disease events.



3.1 Outcome. Total coronary heart disease events [minus 4 biased RCTs]