



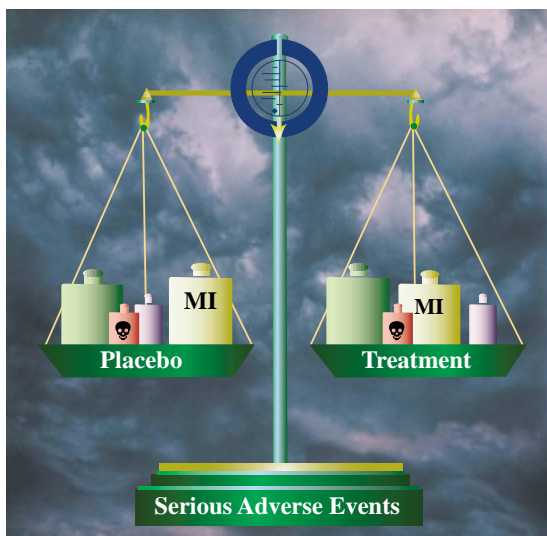

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

**Serious Adverse Event Analysis:
 Lipid-Lowering Therapy Revisited**

A recent paper has documented the under-reporting of safety data in published randomized controlled trials (RCTs).¹ Serious adverse events (SAEs) comprise one component of safety and are potentially the most important outcome measure in RCTs. Regulatory bodies require SAEs to be collected in all clinical trials. **SAEs 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.**² Because total SAEs include benefit and harm, total % SAEs provides a useful single measure of the overall health impact of a particular intervention.

How does SAE analysis relate to the usual way data in RCTs are presented?
 SAE analysis is particularly relevant for RCTs in which the goal of therapy is to reduce death and life-threatening events, such as lipid-lowering therapy trials. Letters #24 and #27 presented the benefit of lipid-lowering therapy in terms of a common outcome: the incidence of total myocardial infarction (MI) or cardiovascular (CV) death. This combined outcome is also included in total % SAEs. If, for example, a statin decreases total MIs or CV deaths and has no serious adverse consequences, the health benefit will be seen as a decrease both in the defined outcome and in % SAEs compared to placebo. If, however, the statin increases other SAEs, in addition to reducing the defined outcome, then total % SAEs may be unchanged or even increased as compared to placebo.

Are SAEs reported in the major lipid-lowering trials?
 SAE data were sought in the major placebo-controlled trials published up to September, 2001 using statins (5 trials)³⁻⁷ or fibrates (5 trials)⁸⁻¹². Remarkably, only one study, the AFCAPS trial,³ reported total % SAEs in the treatment and placebo groups. In this study, lovastatin was compared with placebo in patients without cardiovascular disease (primary prevention). Similar total % SAEs were reported for the lovastatin, 34.2%, and placebo groups, 34.1% (RR = 1.0 [0.94-1.07]). What this indicates is that the 1.4% absolute risk reduction in



total MI or CV death (see Table Letter #27) has been negated by an absolute risk increase in other SAEs. No information is provided as to what these other SAEs might be. The only other trial that reported anything approximating SAEs was the coronary drug project (CDP), a secondary prevention trial. This trial reported the percentage of patients ever hospitalized at 5 years: 55.1% for clofibrate and 52.4% for placebo (RR = 1.05 [0.99-1.12]).⁸

What can be learned from all-cause mortality?
 Total %SAEs can be divided into all-cause mortality and life-threatening events. All-cause mortality was reported in all the trials. Analysis of this outcome is summarized in the Table.

Cerivastatin (Baycol) market withdrawal
Cerivastatin was the most potent statin on the market, effective in fractions of mg quantities. Concern arose as a result of deaths from rhabdomyolysis in the United States, 40% of which were associated with prescribing in combination with gemfibrozil. Deaths linked to cerivastatin continued to be reported despite 2 warning letters to United States doctors advising them to start cerivastatin with the lowest available dose and not to prescribe cerivastatin with gemfibrozil. The decision to remove the drug occurred after 31 rhabdomyolysis deaths had been reported and was based partly on the availability of other statins: lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin. These other statins have been associated with rhabdomyolysis; it is important that such cases be reported to regulatory authorities.

Table. All-cause mortality in major lipid-lowering trials

Trial		Drug %	Placebo %	RR # (95% CI)	ARR/ARI %	NNT/NNH (duration)
Primary statin	WOSCOP Pravastatin ⁴	3.2	4.1	0.78 (0.61-1.01)	NS	NS (4.9 yr)
	AFCAPS Lovastatin ³	2.4	2.3	1.04 (0.76-1.41)	NS	NS (5.2 yr)
	Total			0.88 (0.72-1.06)	NS	NS NS
Primary fibrate	WHO Clofibrate ¹¹	3.0	2.4	1.27 (1.01-1.59)*	0.6	167 (5.3 yr)
	Helsinki Gemfibrozil ¹²	2.2	2.1	1.06 (0.70-1.61)	NS	NS (5.0 yr)
	Total			1.22 (0.99-1.49)	NS	NS NS
Secondary statin	4S Simvastatin ⁵	8.2	11.5	0.71 (0.59-0.85)*	3.3	30 (5.4 yr)
	CARE Pravastatin ⁶	8.6	9.4	0.92 (0.76-1.11)	NS	NS (5.0 yr)
	LIPID Pravastatin ⁷	11.0	14.1	0.78 (0.70-0.88)*	3.1	32 (6.1 yr)
	Total			0.79 (0.73-0.86)*	2.6	38 (5.5 yr)
Secondary fibrate	CDP Clofibrate ⁸	25.5	25.4	1.00 (0.89-1.13)	NS	NS (5.0 yr)
	VA-HIT Gemfibrozil ⁹	15.7	17.4	0.90 (0.76-1.08)	NS	NS (5.1 yr)
	BIP Bezafibrate ¹⁰	10.4	9.9	1.06 (0.86-1.30)	NS	NS (6.2 yr)
	Total			0.98 (0.90-1.08)	NS	NS NS

Calculated using Review Manager 4.1, Cochrane Collaboration. * p < 0.05. NS = Not statistically Significant. RR = Risk Reduction, refers to the % mortality with drug divided by the % mortality with placebo. CI = Confidence Interval. ARR = Absolute Risk Reduction. NNT = Number Needed to Treat to prevent one event. ARI = Absolute Risk Increase. NNH = Number Needed to Treat to cause one Harmful event.

These data demonstrate a significant mortality benefit for statins in secondary prevention (RR less than 1 with confidence intervals not including 1), but not for any of the other clinical settings. A constant percentage of life-threatening events is predictably fatal in any particular RCT. Thus the RR for total mortality should reflect the RR for total SAEs. That is the case for the two instances here; the AFCAPS RR for SAEs, 1.00 [0.94-1.07], and the CDP RR for hospitalizations, 1.05 [0.99-1.12], are similar to the respective mortality RRs in the Table.

Conclusions

- Total %SAEs is an important measure of the health impact of a drug.
- Total %SAEs is often not reported in published RCTs, including lipid-lowering trials.
- **Mortality analysis supports the use of statins for secondary prevention.**
- Analysis of SAEs and mortality does not support the use of statins for primary prevention or the use of fibrates for primary or secondary prevention.

References:

- Ioannidis J and Lau J. *Completeness of safety reporting in randomized trials. An evaluation of 7 medical areas.* JAMA. 2001; 285: 437-443.
- Expert working group (efficacy) of the international conference on harmonization of technical requirements for registration of pharmaceuticals for human use. *Clinical safety data management: definitions and standards for expedited reporting.* Federal Register. 1995; 11284-11287.
- Downs JR, Clearfield M, Weis S, et al. *Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS.* JAMA. 1998; 279:1615-1622.
- Shepherd J, Cobbe SM, Ford I, et al. *Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia.* N Engl J Med. 1995; 333:1301-1307.
- Scandinavian Simvastatin Survival Study Group. *Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S).* Lancet. 1994; 344:1383-1389.
- Sacks FM, Pfeffer MA, Moye LA, et al. *The effect of pravastatin on coronary events after myocardial infarction in patients with*

Landmark Editorial Announcement

In September 2001, thirteen of the major medical journals in the world, including CMAJ, published a common editorial entitled "Sponsorship, Authorship and Accountability".^{13,14} The editors emphasize "Authorship means both accountability and independence. A submitted manuscript is the intellectual property of its authors, not the study sponsor." In addition to the editorial, these journals have revised and strengthened the section on publication ethics in the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals".¹⁵ This example of cooperation amongst the major journals may encourage better reporting of safety data, including SAEs, in published RCTs.

This Letter contains an assessment and synthesis of publications up to September 2001. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

- average cholesterol levels. N Engl J Med. 1996; 335:1001-1009.
- Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels.* N Engl J Med. 1998; 339:1349-1357.
- Coronary Drug Project Research Group. *Clofibrate and niacin in coronary heart disease.* JAMA. 1975; 231:360-381.
- Bloomfield Rubins H, Robins SJ, Collins D, et al. *Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol.* N Engl J Med. 1999; 341:410-418.
- BIP Study Group. *Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The Bezafibrate Infarction Prevention (BIP) Study.* Circulation. 2000; 102:21-27.
- Committee of Principal Investigators. *A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate.* British Heart Journal. 1978; 40:1069-1118.
- Frick MH, Elo O, Haapa K, et al. *Helsinki Heart Study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease.* N Engl J Med. 1987; 317:1237-1245.
- Davidoff F, DeAngelis CD, Drazen JM, et al. *Sponsorship, authorship and accountability.* CMAJ. 2001; 165:786-788.
- Editorial. *Look, no strings: publishing industry-funded research.* CMAJ. 2001; 165:733.
- International Committee of Medical Journal Editors. *Uniform requirements for manuscripts submitted to biomedical journals.* Med Educ. 1999; 33(1):66-78.