Analysis of serious adverse events

Lipid-lowering therapy revisited

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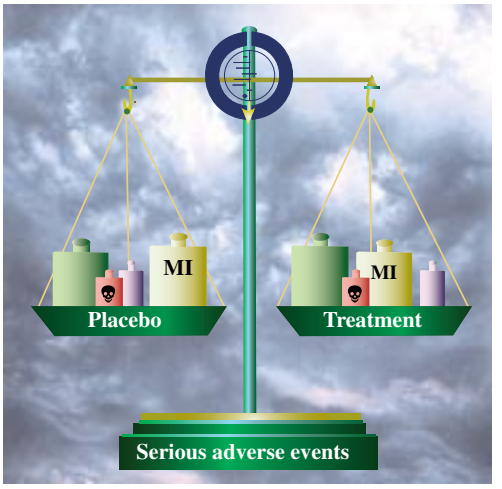
A recent paper documented underreporting of safety data in published randomized controlled trials (RCTs).[1] Serious adverse events (SAEs) are one component of safety and are potentially the most important outcome measure in RCTs. Regulatory bodies require data on SAEs to be collected in all clinical trials.



Serious adverse events include any untoward medical occurrences that result in death, are life-threatening, require hospitalization or prolongation of hospitalization, or result in persistent or severe disability.[2] Because total SAEs include benefit and harm, the total percentage of SAEs provides a useful single measure of the overall health effects of a particular intervention.

Combined outcomes in SAE analysis

Serious adverse event analysis is particularly relevant for RCTs in which the goal of therapy is to reduce death and life-threatening events (eg, lipid-lowering therapy trials). *Therapeutics Letters* no. 24[3] and no. 27[4] presented the benefit of lipid-lowering therapy in terms of a common outcome: incidence of total myocardial infarction (MI) or cardiovascular (CV) death.

This combined outcome is also included in total percentage of 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 in both the defined outcome and in percentage of SAEs compared with placebo. If, however, the statin increases other SAEs, in addition to reducing the defined outcome, then the total percentage of SAEs might be unchanged or even increased as compared with placebo.

Are SAEs reported in major lipid-lowering trials?

We looked for SAE data in the major placebo-controlled trials published up to September 2001 using statins (five trials)[5-9] or fibrates (five trials).[10-14] Remarkably, only one study, the Air Force Coronary Atherosclerosis Prevention Study (AFCAPS) trial,[5] reported total percentage of SAEs in treatment and placebo groups. The AFCAPS trial compared lovastatin with placebo in patients without CV disease (primary prevention). Similar total percentage of SAEs was reported for lovastatin (34.2%) and placebo groups (34.1%) (relative risk [RR] 1.0; 95% confidence interval [CI] 0.94 to 1.07).

What this indicates is that the 1.4% absolute risk reduction for total MI or CV death (see the table in *Therapeutics Letter* no. 27[4]) has been negated by an absolute risk increase in other SAEs. No information is provided as to what these other SAEs are. The only other trial that reported anything approximating SAEs was the Coronary Drug Project, a secondary prevention trial. This trial reported the percentage of patients ever hospitalized

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Table 1. All-cause mortality in major lipid-lowering trials

STATIN AND FIBRATE TRIALS	DRUG (%)	PLACEBO (%)	RISK REDUCTION* (95% CONFIDENCE INTERVAL)	ABSOLUTE RISK REDUCTION OR ABSOLUTE RISK INCREASE	NNT TO PREVENT ONE EVENT OR NNT TO CAUSE ONE HARMFUL EVENT (DURATION IN Y)
PRIMARY STATIN					
WOSCOP pravastatin[6]	3.2	4.1	0.78 (0.61-1.10)	NS	NS (4.9)
AFCAPS[4] lovastatin[5]	2.4	2.3	1.04 (0.76-1.41)	NS	NS (5.2)
TOTAL			0.88 (0.72-1.06)	NS	NS
PRIMARY FIBRATE					
WHO clofibrate[13]	3.0	2.4	1.27 (1.01-1.59)	0.6	167 (5.3)
Helsinki gemfibrozil[14]	2.2	2.1	1.06 (0.70-1.61)	NS	NS (5.0)
TOTAL			1.22 (0.99-1.49)	NS	NS
SECONDARY STATIN					
4S simvastatin[7]	8.2	11.5	0.71 (0.59-0.85)†	3.3	30 (5.4)
CARE pravastatin[8]	8.6	9.4	0.92 (0.76-1.11)	NS	NS (5.0)
LIPID pravastatin[9]	11.0	14.1	0.78 (0.70-0.88)†	3.1	32 (6.1)
TOTAL			0.79 (0.73-0.86)†	2.6	38 (5.5)
SECONDARY FIBRATE					
CDP clofibrate[10]	25.5	25.4	1.00 (0.89-1.13)	NS	NS (5.0)
VA-HIT gemfibrozil[11]	15.7	17.4	0.90 (0.76-1.08)	NS	NS (5.1)
BIP bezafibrate[12]	10.4	9.9	1.06 (0.86-1.30)	NS	NS (6.2)
TOTAL			0.98 (0.90-1.08)	NS	NS

NNT—number needed to treat, NS—not statistically significant.
**Risk reduction is percentage mortality with treatment divided by percentage mortality with placebo (calculated using Review Manager 4.1, Cochrane Collaboration).*
†*P< .05.*

by 5 years after the trial: 55.1% in the clofibrate treatment arm; 52.4% in the placebo group (RR 1.05; 95% CI 0.99 to 1.12).[10]

What can be learned from all-cause mortality?

Total percentage of SAEs can be divided into all-cause mortality and life-threatening events. All-cause mortality was reported in all trials. Analysis of this outcome is summarized in **Table 1**.[5-14]

These data demonstrate a substantial benefit in regard to mortality for statins in secondary prevention (RR <1; 95% CI not including 1), but not for any 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 was 1.00, and the Coronary Drug Project's RR for hospitalizations was 1.05; both are similar to respective mortality RRs in **Table 1**.[5-14]

Conclusion

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

Acknowledgment

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Cerivastatin (Baycol) market withdrawal

Cerivastatin was the most potent statin on the market, effective in fractions of mg. 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 two 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.

Landmark editorial announcement

In September 2001, 13 of the major medical journals in the world, including the *Canadian Medical Association Journal*, published a common editorial entitled "Sponsorship, Authorship and Accountability."[15,16] The editors emphasized, "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".[17] This cooperation among the major journals might encourage better reporting of safety data, including SAEs, in published RCTs.

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Reproduced from Therapeutics Letter *2001;42:1-3 (***www.ti.ubc.ca***). 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. We invite your comments. Please contact Jim Wright by e-mail at* **jmwright@interchange.ubc.ca** *or by fax at (604) 822-0701.*