THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Evidence Based Drug Therapy

What Do the Numbers Mean?

Imagine you just discovered that you have a risk factor for cardiovascular disease (e.g. High LDL cholesterol). A drug that will reduce this risk factor is available, and it has a low incidence of side effects. Consider the 3 following scenarios. Would you be willing to take this drug daily for the next 5 years if significant results from randomised placebo controlled trials showed that:

1 patients taking this drug for 5 years have 34% fewer heart attacks than patients taking placebo; **or**

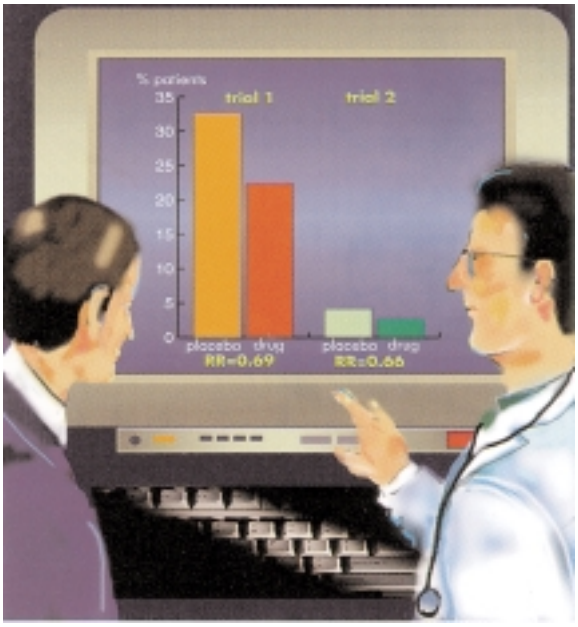
2 2.7% of the patients taking this drug for 5 years had a heart attack, comparing to 4.1% taking a placebo, a difference of 1.4%; **or**

3 if 71 patients took this drug for five years the drug would prevent one from having a heart attack. There is no way of knowing in advance which person that might be.

Did you make the same decision for all three scenarios? If not, you were fooled by the numbers, because the three scenarios represent the same data from the same trial presented to you in three different ways.[1,2]

• *Why do you and your patients need to know the difference between relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NTT)?*

Benefits in clinical trials are most often presented in trial reports and advertisements as RR (risk ratio) or RRR; these can often be misleading to clinicians and patients. In fact, clinicians and patients make different drug therapy decisions, depending on the way the results are presented; **in the example shown above fewer physicians[1] and patients [2] will choose the therapy when the data is presented as ARR and NNT than if it is presented as RR or RRR.** Table 1 demonstrates how the different terms are calculated and the practicall implications of this concept. In this example the RR and the RRR are similar, yet the overall results are quite different. The ARR and NNT give a much better appreciation of the magnitude of the benefit and of the potential



for a positive impact in your practice. Other essential parameters to be considered are the importance of the outcome to the patient and the time required to achieve the benefit. (see Table 2). **It is tempting but inappropriate to extrapolate benefits beyond the duration of the trial.**

• *How can you and your patient make the most informed decision?*

For most drug therapy trials ARR and NNT are easily calculated from the data presented in the paper. Risks of a drug therapy can also be calculated as absolute risk increase, or NNT to cause an adverse event. When dealing with individual patients, it is important to realise that patients differ markedly in their attitude toward taking medications. It is therefore essential that the practitioner is able to explain the benefits and risks of a treatment in a form that the patient can understand. Often the NNT to prevent or cause events in a specified period of time are the most meaningful. Once the patient understands the potential benefits and risks of therapy, a joint decision can be made. To help guide the clinician and patient, Table 2 outlines the use of these numbers to present some of the evidence for 7 common clinical scenarios (including the examples in Table1).

Table 1: An example of similar relative risks but different absoulte risk reductions [4,7]

Placebo # of patients Total	Event	Drug # of patients Total	Event	Relative Risk• RR	Relative Risk Reduction■ RRR	Absolute Risk Reduction* ARR	Number Needed to Treat# NNT
3178	1038	3810	854	854/3810 = 0.69 1038/3178	(1-0.69)x100=31%	32.6%-22.4%=10.2%	100/10.2=10
2030	84	2051	56	56/2051 = 0.66 84/2030	(1-0.66)x100=34%	4.1%-2.7%=1.4%	100/1.4=71

• Relative risk (RR)= Event rate (Drug) / Event rate (Placebo)

■ Relative risk reduction (RRR) = 1- relative risk x 100

* % Absolute risk reduction (ARR) = % Event rate (Placebo) - % Event rate (Drug)

Number needed to treat (NNT) = 100/ % absolute reduction

Table 2: Examples of Evidence of Benefit of Common Drug Therapies *

Clinical trial (measured outcome events)	Event incidence %		RR	RRR %	ARR %	NNT	Trial duration years
	Placebo	Drug					
ACE inhibitors for congestive heart failure [4] (total mortality or hospitalisation for CHF)	32.6	22.4	0.69	31	10.2	10	~0.5
Diuretics and beta blockers in old patients with hypertension[6] (total mortality or cardiovascular event)	22.5	13.7	0.61	39	8.8	11	5
Simvastatin for elevated cholesterol in patients with coronary heart disease [5] (total mortality or coronary event)	31	22.6	0.73	27	8.4	12	5
Long-term beta blockers after myocardial infarction [7] (total mortality or non-fatal reinfarction)	17.6	13.7	0.78	22	3.9	26	~0.5
Gemfibrozil in male patients with high cholesterol [8] (total coronary events) •	4.1	2.7	0.66	34	1.4	71	5
Aspirin in healthy male physicians [9] (total myocardial infarctions)	2.2	1.3	0.56	44	0.9	111	5
Misoprostol in rheumatoid arthritis patients taking NSAIDs [10] (serious gastrointestinal complications)	0.95	0.57	0.60	40	0.38	263	~0.5

RR = Relative Risk RRR = Relative Risk Reduction ARR = Absolute Risk Reduction NNT = Number Needed to Treat
* Inclusion in the table does not necessarily imply endorsement by the Therapeutics Initiative.
• Total mortality not included because not statistically different; if total mortality were added NNT is even greater.

• What is evidence Based Drug Therapy?

Evidence based drug therapy means **integrating the best evidence, the individual characteristics of the patient, and individual clinical expertise, into a decision making process which leads to optimal drug therapy.**[3] This is a complex process that requires a detailed understanding of the evidence, including how the evidence was derived and an appreciation of the magnitude of the benefits and/or risks.

• How does the Therapeutics Initiative compile the evidence that is presented in the Therapeutics Letter?

First, a search is done to determine whether other groups arund the world have done a recent "systematic review" (meta-analysis) of the subject. We only use systematic reviews that meet rigorous scientific standards (e.g. those done by the Cochrane Collaboration). When other systematic reviews are not available, we do a comprehensive literature search and compile the relevant published trials. We limit ourselves to the best evidence, **the randomised-controlled, double-blind clinical trial, or meta-analysis of randomised controlled trials**, whenever possible. We try to focus on trials that measure the true goal of therapy (e.g. morbidity and mortality) and not surrogate markers (e.g. blood pressure), and exclude trials with major methodological flaws. When this is done the number of trials that need to be extensively critiqued is limited and manageable. Our recommendations are based on the best trials, the most important of which we include in oir reference list. Before the Letter is sent out, a draft is reviewed by the members of the Advisory and Scientific Information and Education Committees of the TI, representatives of the B.C. College of Family Practice, and specialists in that particular therapy. All suggestions are considered and included if substantiated by evidence. Once published, we welcome feedback. Drug therapy is a rapidly changing filed and we are always open to new evidence or evidence that we may have overlooked.

• What if the evidence is inconclusive?

Unfortunately, this situation is frequently the case. The only available evidence may be based on surrogate endpoints, cohort studies, case control studies, or sub-group analyses of randomised controlled trials. Such forms of evidence are interesting and hypothesis generating, but are not conclusive. A good example of this is the evidence for long-term menopausal hormone therapy presented in Letter 14. **In such cases it is important that the proper experiment, a randomised controlled trial, is done, and that the practitioner and patient be aware that the evidence is not conclusive at present.**

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