Editorial

Evidence-Based Medicine: Progress but Not a Final Solution

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Convincing evidence of the beneficial effects of a treatment used to be provided by the consistency with which it relieved symptoms and abnormal findings and/or prolonged survival. The beneficial effects of diuretics for relieving fluid accumulation in patients with cardiac failure and those of bypass surgery or angioplasty for improving effort tolerance in patients with flow-limiting coronary stenoses were so obvious and consistent that there had been no need for large multicenter trials.

However, the benefit of some treatments may not be obvious, and therefore the consistency of their effect may be uncertain: this may occur when a treatment has only a moderate effect (or additional effect) on the pathogenetic mechanisms of the disease, or when the underlying disease causes only mild symptoms and abnormalities and is seldom associated with adverse events. In the past, the choice of such treatments was left to a sort of clinical freedom, or even worse, of clinical anarchy: it was based on personal experience or, worse, on opinions.¹

The advent of randomized clinical trials represented a major, rational step forward because trials provide a statistically based quantitative comparison of average benefits and side effects of the treatments tested. Nowadays, multicenter, randomized trials are indeed the acid test for any therapeutic hypothesis derived from experimental findings or from pilot studies: they have become the basis of “evidence-based medicine.” This concept is now gaining a wide acceptance because it provides useful standards of care and protects from malpractice allegations.

The design of trials, their statistical analysis and meta-analysis have become so sophisticated that major journals were compelled to recruit statisticians onto their editorial boards.

I therefore accept the conclusions of statisticians, but the proliferation of very large trials with broad inclusion criteria is, in my opinion, grounds for concern for practicing cardiologists and for the economics of health care.

For practicing cardiologists, the concern is related to the fact that the growing use of megatrials rapidly increases the number of treatments that produce a statistically significant improvement in prognosis within the same broad group of patients. For example, five different preventive strategies (i.e., anticoagulation, rehabilitation, beta blockade, cholesterol reduction, and use of antiplatelet agents) were shown to produce a statistically significant reduction in mortality, ranging from 14 to 22% in a meta-analysis of secondary prevention trials in patients postmyocardial infarction (MI).²

Should practicing cardiologists prescribe all treatments proven to be beneficial in megatrials to all patients post MI? Forever?

If the percent reduction of risk demonstrated by all trials in patients post MI could be cumulated, the total reduction of risk would be much greater than 100%. This suggests that the patients who benefit from the various forms of treatment are not necessarily the same. If it may not be reasonable to prescribe all patients each treatment proven to be beneficial in a megatrial, practicing cardiologists may be led to return to “clinical freedom” for their choices.

For the economics of health care, the concern is related to the fact that the larger the number of patients who have to be included in a trial to prove a statistically significant benefit, the smaller the absolute benefit.¹ A large percentage reduction in mortality that reaches statistical significance in only very large trials suggests either a relatively low rate of preventable adverse events in randomized patients or a considerable heterogeneity of patients enrolled, only a few of whom are susceptible to the benefits of the treatment. A large heterogeneity of patients implies a “dilution effect” of those susceptible to the benefits of treatment by those who are not susceptible and hence are treated unnecessarily.

Indeed, the concept of evidence-based medicine has a hidden assumption: it tacitly implies that the average benefit documented in the trial applies equally to all patients who meet the inclusion criteria. This assumption may not be valid when the pathogenetic mechanisms of the disease are multiple and incompletely known.

The same rigor that statisticians on editorial boards demand for the analysis of the data should also be demanded for the

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Received: March 23, 1998

Accepted: March 23, 1998

assessment of the homogeneity of the patients enrolled in megatrials in terms of major pathogenetic components.

My concern about the possible heterogeneity of cardiac patients currently included in megatrials with very broad inclusion criteria will become clearer if we consider what could happen in the field of hematology if the pathogenetic mechanisms of anemia were still as obscure as those of infarction, unstable angina, sudden death, coronary restenosis following percutaneous transluminal coronary angioplasty (PTCA), and so forth. The hematologists could design a megatrial enrolling 10,000 patients with hemoglobin levels < 10 g%: 5,000 randomized to treatment with vitamin B12 and 5,000 to placebo for 1 year. If a sufficiently large number of B12-deficient patients happened to be in the group, the statistical analysis of the results would demonstrate that after 1 year treated patients on average had a highly significant increase in hemoglobin concentration. The industry that financed the trial and perhaps even the Food and Drug Administration (FDA) would be pleased with the results. However, the average increase in hemoglobin would merely be the result of the benefit produced in B12-deficient patients. If only B12-deficient patients were included in the trial, a much smaller number would have been sufficient to prove the benefit, as the average result would not have been diluted by the inclusion of patients who could not receive any benefit from the treatment. Obviously the FDA would have approved the treatment only for B12-deficient patients, not for all anemics.

The same reasoning would apply to other trials testing the benefit of iron or of folic acid supplements in unselected anemic patients.

This line of reasoning may indeed apply to very topical cardiological scenarios.

We have no evidence that all patients post MI are equally susceptible to the benefit of cholesterol-lowering drugs, of new more powerful antithrombotic agents, of ACE-inhibitors, of beta blockers, or of calcium-channel blockers.

When setting up trials to demonstrate a reduction of the rate of restenosis following PTCA, it would be desirable not to include the 60% of patients who do not restenose anyway,

and it would be useful to ascertain whether the cause of restenosis is the same in all those who restenose.

When testing more powerful thrombolytic agents or primary PTCA for patients with acute MI, it would be desirable not to include those patients who respond rapidly also to the combination of aspirin and streptokinase. At present, there is little incentive to undertake research to try to separate responders from nonresponders, as it is undoubtedly difficult. A blanket treatment for all those who meet current very broad inclusion criteria is appealing to the industry and to practicing physicians.

However, the cardiological community can no longer afford the indiscriminate application of preventive treatments for patients who may not be susceptible to the benefit; nor can it afford the indiscriminate application of new or more aggressive and more costly forms of treatment to patients who could obtain the same benefit from available treatments: there may be no money left to treat those who really need it. The new challenge for the cardiology community is the precise identification of specific subsets of patients in whom the greatest absolute reduction of risk can be expected from a particular or new treatment, but cannot be obtained by simpler or less expensive means.

The financial resources required to fund the research for distinguishing responders from nonresponders is unlikely to be provided by the industry, which understandably wishes its products to be as broadly indicated as possible and hence is inclined to finance trials with very broad inclusion criteria. Health care providers may find it less expensive to finance research aimed at the identification of responders and nonresponders than to pay for all treatments for all patients.

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