Treatment of dyslipidemia: We don't know all we think we know

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At the population level, the magnitude of the benefit and cost of a preventive intervention depends on three factors: the baseline risk of the person who receives the intervention, the effect size of the intervention and the long-term compliance with the intervention. The corollary of this statement is that there must be a line under which the risk is so low that the risk to benefit ratio is not acceptable for the individual patient and, most importantly, where the resources used to treat these very low-risk individuals could be used more efficiently somewhere else in the health care system. This is assuming, of course, that the politicians and public servants to whom we have delegated the administration of our health care system make the right decisions.

In the context of cardiovascular prevention, I will briefly review our knowledge of the three above-mentioned components at both the population and individual level. My intent is to review the quality and real-life applicability of the available evidence, to show that it is a great deal hazier than many seem to believe, and to propose courses of action that would take into consideration the lack of a firm scientific foundation.

BASELINE CARDIOVASCULAR RISK

The baseline risk is defined as the risk of a cardiovascular event at the time the preventive intervention is applied to an individual patient.

In the case of patients who have already suffered a cardiovascular event, the risk of a second event is quite high. Most students of the disease agree that abnormal lipid levels in these patients should be treated, although there is still disagreement as to what constitutes abnormal lipid levels and how aggressively they should be treated.

The main point of contention is whether the pharmacological treatment of dyslipidemias should be restricted to secondary prevention, which is arbitrarily defined by the occurrence of a cardiovascular event. Contrary to what some individuals seem to believe, the problem is quite complex and, like all complex problems, it has a simple solution that, unfortunately, is usually wrong. In the case of using lipid-modifying agents to prevent cardiovascular disease, the simple solution entails restricting treatment to secondary prevention — that is, treat only the patients who have already had a cardiovascular event.

The fallacy of the primary versus secondary prevention concept

This arbitrary, dichotomous division may be valid in infectious diseases, where the patient is well one day and develops a pneumococcal pneumonia the following day. In the field of atherosclerosis, however, the concept is deeply flawed and can

only lead to misleading conclusions. Surely, no student of this disease thinks that a patient has perfectly normal coronary arteries on the day, the week or even the five to 10 years preceding his or her first myocardial infarction. The classical studies of coronary artery disease in combat casualties of the Korean (1) and Vietnam (2-3) Wars showed the presence of advanced coronary disease in presumably healthy young men. More recently, Iannuzzi et al (4) reported increased intima-media thickness in obese children six to 14 years of age.

Thus, it is quite clear that atherosclerosis is a disease that begins early in life, and that it can be quite severe by the time the first coronary event occurs. The occurrence of a clinical coronary event should not be used as the defining factor that establishes whether prevention is a worthwhile endeavour. It is an important risk factor — arguably the most important — but it is by no means the definitive one.

Once it is accepted that the lipid levels of some patients should be treated before the first clinical coronary event, one still has to determine who these patients are.

The risk of determining cardiovascular risk using the Framingham equations

The pharmacological treatment of dyslipidemia usually relies on the Framingham equations to determine cardiovascular risk in the context of primary prevention. The Framingham risk factors are sex, age, smoking, systolic arterial blood pressure and high-density lipoprotein cholesterol. There are a number of important risk factors considered to be major by the American Heart Association (5) but are not included in the Framingham equations: the metabolic syndrome; obesity (particularly abdominal obesity); physical inactivity; and family history of premature coronary artery disease. Furthermore, the Framingham equations do not include ethnic characteristics, psychosocial factors, small low-density lipoprotein particles, elevated triglycerides, homocysteine, lipoprotein A, fibrinogen or C-reactive protein. Risk factors presently recognized as important and in some cases very significant, such as the metabolic syndrome, are not included in the equations derived from the Framingham data. The application of the Framingham equations to a modern-day patient can thus result in an underestimation of his or her real cardiovascular risk. Predictive equations based on the whole spectrum of cardiovascular risk factors, as identified by Yusuf et al (6) in the INTERHEART study, should be considered. These data should lead to patient-based, practitioner-friendly guidelines on global cardiovascular prevention. Such guidelines would be much more useful to the general practitioner than the traditional 'balkanized' guidelines dealing individually with specific risk factors such as dyslipidemia or hypertension.

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EFFECT SIZE

The effect size in the clinical trials

The effect size, obtained in ideal patients treated under very artificial circumstances, is provided by the results of large clinical trials. In the case of beneficial interventions, it is usually expressed as a reduction in relative risk, a statistic that gives the impression (illusion?) of the largest possible effect size. The obvious problem with relative risk is that it does not take into consideration the magnitude of the baseline risk. The absolute risk reduction (which some of us prefer to call the risk difference) has been proposed as a more appropriate measure of effect size. The number needed to treat (NNT) is a spin-off from the absolute risk difference. Contrary to what many people seem to believe, NNT is not a measure of risk reduction, but rather one of economical efficiency (the ratio of the effective or useful output to the total input in any system). As such, the NNT would be the first, but hopefully not the last, step of a formal pharmacoeconomical study. The use of the NNT as the definitive and final measure of economic efficiency should be avoided because it can lead to gross misunderstandings and potentially deleterious public health decisions. In my view, the problem resides in the obsession with expressing the effect size with a single measure (relative risk, hazard ratio, absolute risk difference or the NNT) when, in fact, proper and useful communication can only be achieved if one has access to its two components: the risk in the exposed and the risk in the unexposed, or the risk in those exposed to drug A and the risk of those exposed to its comparator (placebo or another drug).

For instance, let us assume that the results of a hypothetical randomized clinical trial show that all-cause mortality is 10% in the placebo group and 8% in the patients who received drug A. The results of such a trial will be reported and quoted as follows: risk ratio=0.80; thus, drug A produces a 20% decrease in mortality. The main problem with this expression of the result of the trial and, consequently, of the benefit of the drug, is that a trial where mortality is 1% in the placebo group and 0.8% in the drug B group would yield exactly the same risk ratio and estimate of benefit as drug A — that is, a 20% decrease in mortality. Intuitively, it is quite obvious that these two drugs do not have similar benefits. An alternative would be to express the benefit with the difference in the absolute risk of the two treatment groups; for drug A, it would be 2 (10—8), and for drug B, it would be 0.2 (1—0.8). Because these numbers are not very impressive, it is not surprising that most authors (and this is true irrespective of the source of the funds) prefer to express their result as a 20% improvement. Although the absolute risk difference is considered by many as more meaningful than the risk ratio, it does not, by itself, provide complete, clinically meaningful information. A much more intuitively understandable approach, and therefore one that is more applicable to clinical practice, would be the following: drug A decreases mortality from 10% to 8%, and drug B decreases mortality from 1% to 0.8%.

REAL-LIFE PATIENTS AND COMPLIANCE

Most clinical trials of pharmaceutical interventions are designed and implemented to demonstrate the superiority of drug A over drug B. To achieve this objective, trialists will often use very 'tight' inclusion and exclusion criteria. The population on which the trial is done can thus be a small sample of

the population to which the trial results will eventually be applied. Considerable extrapolation will often have to be done by the physician, who has to make therapeutic decisions on a patient who, for a variety of reasons, would not have met the inclusion and exclusion criteria of the keystone trial.

Of particular importance in this regard is the fact that compliance or persistence with therapy is much worse in real life than in the clinical trials (7-8). The premature discontinuation of pharmacological therapy that one so often sees in real-life patients constitutes a huge waste of resources and of the opportunity of benefit. The very early discontinuation of preventive pharmacological therapy by a high-risk patient most probably results in a higher waste of resources than the faithful compliance of a counterpart with a smaller cardiovascular risk. The development of scientific evidence capable of guiding the physician to better understand and predict noncompliance with preventive therapy and the interventions most likely to improve it, such as those developed by Lalonde et al (9), should be a high priority.

CONCLUSION

The scientific data are too hazy, and their application to an individual patient too uncertain, to allow the drawing of a treat/don't treat line that would be applicable to a whole population. Particularly abhorrent would be the arbitrary division between primary and secondary prevention. For the time being, individualization of therapy based on the many factors that are only known by the physician and his or her patient should be the order of the day.

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