

Gambling with cardiovascular risk: picking the winners and the losers

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The number of successful lipid-intervention trials is on the increase, and evidence is accumulating that lipid modification can reduce the risk of cardiovascular events among individuals with only modest degrees of blood-lipid abnormalities.¹⁻⁴ The number of adults targeted for lipid therapy is therefore bound to increase in the coming years. Although this growth may be scientifically sound, it may not be clinically feasible or economically affordable. Accordingly, consensus guidelines and expert panels have recommended targeting of interventions towards those individuals at highest risk of disease so as to maximise the benefits that are realised and to get "the biggest bang for our bucks".^{5,6} The question is whether those who will benefit the most can be identified accurately, and if so, where should the line to initiate treatment be drawn.

Cardiovascular risk assessment has tremendous potential, but the future cannot be predicted with any real certainty for the individual presymptomatic patient. When considering primary prevention among 1000 adults with a 20% 10-year risk of developing cardiac disease, neither the 200 potential losers nor the 800 potential winners can be identified. Nonetheless, multivariate risk equations from studies such as the Framingham Heart Study can discriminate between high-risk and low-risk subgroups among whom the incidence of future events will vary substantially.^{7,8} These data have also been shown to forecast accurately the absolute risk of future events in clinical trials and to predict the benefits of lipid interventions.⁹

In view of the potential strengths of the epidemiological data, the challenge is to "operationalise" this information such that patients and physicians can make informed decisions. In this issue of *The Lancet*, Paul Durrington and colleagues have systematically shown that different expert panels can assimilate the same epidemiological and clinical trial data and yet produce guidelines with widely differing results. Explicit calculation of cardiac risk has been proposed as one solution, but small simplifications such as not actually measuring HDL-cholesterol concentrations can seriously undermine the accuracy of the final results.¹⁰ This study once again shows the importance of including HDL-cholesterol concentrations in decisions on lipid screening and treatment.

If cardiovascular risk assessment is the way to go, can there be agreement on an absolute risk at which lipid therapy should be initiated? The answer is no, for several reasons. Firstly, the benefits of treating any risk factor depend not only on the absolute risk of future disease but also on the degree to which the risk factor in question contributes to this risk. Lipid therapy for high-risk individuals with a low LDL/HDL ratio but with other risk factors may be less effective than treatment of lower-risk individuals who have a very high ratio but no other risk factors.⁹

Secondly, the threshold for treatment must also be based on the extent to which LDL and HDL concentrations can be changed. When Davey-Smith and colleagues suggested a treatment threshold based on an annual risk of cardiac mortality exceeding 3%, they recognised that their analyses, based on lipid trials published up to 1993, did not include the greater impact on LDL and HDL concentrations that would be

achievable in the near future.⁵ With increasingly powerful drugs to modify blood lipids, the potential concentrations at which to initiate treatment and the appropriate target concentrations are rapidly changing. This change is driven in large part by successful clinical trial results that have not yet identified the lipid concentrations at which the benefits taper off.

Finally, there are the limitations of short-term risk assessment. Primary prevention lasts a lifetime, whereas a calculated 10-year risk summarises a much shorter time horizon. This short time interval favours treatment for older individuals, among whom the immediate absolute risk of disease is high partly because of their age.¹⁰ However, the very fact that older individuals have not yet developed symptomatic disease shows that they have tolerated their risk factors and, with increasing years, should be classified among the winners. On the other hand, younger individuals with serious lipid abnormalities may have a short-term absolute risk of disease below a prespecified threshold, yet this group is the one in which treatment may be most beneficial over the long term.⁹ Moreover, these individuals are at increased risk of premature disease.

In summary, it is not easy to identify a simple risk threshold at which lipid therapy should be started. Nonetheless, cardiovascular risk assessment is a useful scientific exercise and a potentially important addition to doctors' diagnostic and prognostic medical black bags. If nothing else, it provides a framework to help clinicians to inform otherwise healthy individuals that their risk is increased and to help these individuals to make informed decisions about their options.¹¹ Clearly, the poor compliance with lipid therapy outside of clinical trials suggests that patients who start treatment are not convinced of its benefits.¹² Cardiovascular risk assessment is one tool to communicate not only risk but also benefits.

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