Two decades of progress in preventing vascular disease

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In the mid-1950s, myocardial infarction and strokes (vascular events) were not considered to be preventable. This view persisted until the early 1980s. Over the past two decades, reliable data have emerged indicating that smoking cessation, β-blockers, antithrombotic agents, inhibitors of angiotensin-converting enzyme (ACE), and lipid-lowering agents (today's HPS results), each reduce the risk of vascular events to a moderate but important degree. Today's issue of The Lancet has two reports from the MRC/BHF Heart Protection Study (HPS), a large and well-designed 2×2 factorial randomised trial that reliably evaluates the effects of cholesterol-lowering with simvastatin and a cocktail of antioxidant vitamins in preventing vascular events. The results of cholesterol-lowering with simvastatin are a culmination of experimental and epidemiological studies as well as randomised trials over the past 30–40 years. Early trials of cholesterol-lowering were not convincing because the available interventions (drugs or diet) lowered cholesterol to only a modest degree, the interventions were not well-tolerated, or the studies lacked adequate statistical power. With the discovery of statins, large reductions in cholesterol concentrations were easily and safely achievable, and this finding led to a series of trials that demonstrated benefits in selected populations. The MRC/BHF-HPS extends the knowledge to much broader populations. A 1 mmol difference in LDL led to a 25% reduction in relative risk of vascular events (coronary heart disease and strokes) overall. This reduction is probably an underestimate of the true benefits that 40 mg simvastatin would confer, because a substantial proportion of patients in the placebo group also received a statin as the results of other trials became available during the HPS. Therefore, the real benefits are likely to be somewhat larger, perhaps around a one-third reduction in relative risk.

Clear benefits were also seen in several subgroups of patients who were poorly represented in previous trials. These subgroups include those over 75 years of age, women, those with concentrations of LDL below 2·5 mmol/L, individuals with diabetes and no vascular events, and those with known cerebrovascular or peripheral arterial disease. The reduction in ischaemic stroke, without an excess of haemorrhagic stroke is noteworthy, and confirms the findings from previous trials. The reductions in vascular events were observed in addition to other effective therapies, such as aspirin, β-blockers, and ACE inhibitors.

The implications of these findings are profound. Cholesterol-lowering with a statin is of value in much broader populations than currently recognised, including those with “low” and “normal” lipid values. Thus, practically all patients with vascular disease today in western countries will benefit from statins. Perhaps clinicians will choose to initiate and continue treatment with statins in high-risk individuals without routine lipid measurements. The extremely low rates of myopathy and increases in liver enzymes confirm the safety of simvastatin used at 40 mg a day. The lack of liver toxicity suggests that in most patients, muscle or liver enzymes need not be measured routinely. Minimising measurements of lipids and muscle or liver enzymes will simplify the clinical use of statins, and reduce the costs associated with their use. The current results from the HPS study on efficacy and safety were obtained with simvastatin at 40 mg a day. Higher doses of simvastatin may not be as safe, and the recent withdrawal of cerivastatin on safety grounds emphasises the importance of using specific drugs at doses proven to be both effective and safe.

The HPS trial, with three other major trials, also shows the lack of efficacy of antioxidant vitamins in preventing vascular complications. Indeed the small increases in LDL and triglycerides with vitamins in HPS call for caution, as it could well be that prolonged use of these antioxidant vitamins (at least in western populations without nutritional deficiencies) is not only ineffective but may also potentially lead to some increase in vascular disease. Therefore the routine use of such vitamins in large doses should be discouraged.

The lack of benefit of antioxidant vitamins in several large randomised trials contradicts the claims from observational studies that suggested protection against cardiovascular disease and cancers. Several other contradictions between the randomised trial results and the observational data are highlighted by the HPS results. For example, observational studies have described a consistent relation between lipid concentrations and ischaemic strokes, and some have even suggested an increase in haemorrhagic strokes at low concentrations of lipid. Yet an important reduction in ischaemic strokes, with no excess in haemorrhagic strokes, is seen with lipid-lowering in the HPS trial. Furthermore, observational studies have suggested lower rates of fractures with statins and vitamins, higher rates of obstructive airways disease at low cholesterol concentrations, lower rates of cataracts, and lower rates of dementia with both interventions—yet none of these observations have been confirmed by randomised trials, including HPS. These apparent contradictions are likely due to confounding from other factors that may be
associated with use of vitamins or statins, which cannot be adequately adjusted for in observational studies. These findings emphasise the need to generally view claims of treatment benefit from observational studies with considerable scepticism, unless confirmed by large well-designed randomised trials. The past 25 years have seen the establishment of aspirin, β-blockers, ACE-inhibitors, and lipid-lowering therapies to lower the risk of future vascular events, by about a quarter each, in high-risk patients (panel). The benefits of each intervention appear to be largely independent, so that when used together in appropriate patients it is reasonable to expect that about two-thirds to three-quarters of future vascular events could be prevented. Add to this the potential benefits of quitting in smokers (which lowers the risk of myocardial infarction by about one-half after about 2 years). So, in smoker with vascular disease, quitting smoking and use of four simple preventive strategies could theoretically have large potential benefit (say around 80% relative risk reduction).

Potential cumulative impact of four simple secondary-prevention treatments

<table>
<thead>
<tr>
<th>Relative-risk reduction</th>
<th>2-year event rate</th>
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<tbody>
<tr>
<td>None</td>
<td>8%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>25%</td>
</tr>
<tr>
<td>β-blockers</td>
<td>25%</td>
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<tr>
<td>Lipid lowering (by 1-5 mmol)</td>
<td>30%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>25%</td>
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Cumulative relative risk reduction if all four drugs are used is about 75%

Potential cumulative impact of four simple secondary-prevention treatments

Events=cardiovascular death, myocardial infarction, or strokes. To calculate cumulative risk reduction, multiplicative scale was used—eg, two interventions each reducing the risk of event by 30% would be expected to have about 50% relative risk-reduction (1−0·70×0·70). No interactions in treatment effects are observed in trials suggesting that proportionate risk-reduction of specific drug in presence or absence of other effective interventions would be expected to be similar. Smoking cessation lowers risk of recurrent myocardial infarction by about one-half after about 2 years. So, in smoker with vascular disease, quitting smoking and use of four simple preventive strategies could theoretically have large potential benefit (say around 80% relative risk reduction).

Conflict of interest statement

I receive research grants from governmental and charitable organisations, and several pharmaceutical companies for a range of research, including from Merck-Frosst, Canada, for the long-term follow-up of the SOLVD trial participants, and epidemiological studies in diverse ethnic populations (SHARE study). I collaborate with some of the HPS investigators.

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Evidence of success in HIV prevention in Africa

If HIV prevention programmes work, HIV incidence should drop. The problem has been in measuring such an effect. Monitoring HIV incidence directly is difficult, since it requires individuals to present to testing services on more than one occasion. Biases from loss to follow-up and migration in and out often compromise the validity of cohort studies. If these studies are to inform our knowledge of incidence trends, then they must report on trends in a representative population over many years. Such studies are uncommon, and have mostly been in high-risk groups such as sex workers or homosexual men.

In most countries, HIV incidence is instead monitored indirectly through a system of sentinel surveillance of HIV prevalence. Unfortunately, there is not a simple and predictable relation between prevalence, as measured by sentinel surveillance, and incidence in the population. Consensus on what constitutes an accurate and feasible surrogate measure of HIV incidence is essential in assessing what works in HIV prevention.

HIV sentinel surveillance requires frequent data collection, having the appropriate populations under surveillance, consistency over time, and representative sampling. African countries with the most severe HIV epidemics have been judged to have fully implemented sentinel surveillance. In such countries, pregnant women have been targeted in the belief that their prevalence largely reflects that in all sexually active women, provided contraceptive use is low. However, the accuracy of this sentinel surveillance in reflecting population incidence has been challenged, because it includes only those women who attend antenatal clinics and because HIV infection is known to be associated with lower fertility. It has been estimated that the prevalence of HIV infection in pregnant women underestimates the prevalence in the general population prevalence by 35–65% in populations with low use of contraception.

In using prevalence as a surrogate measure of HIV incidence, attention is now focused on women aged 15–24. There are several reasons for this. First, the biases...