nificantly reduced its incidence.³ Importantly, in this group of patients (those undergoing general surgical and orthopaedic procedures, and at risk and immobile medical patients) the incidence of pulmonary embolism fell significantly. The review does not suggest that antiplatelet agents should replace subcutaneous heparin for routine prophylaxis, but, interestingly, the combination of heparin and an antiplatelet agent may be better than heparin alone in preventing pulmonary embolism. This conclusion is based on a small number of trials, and further studies are clearly needed to determine the exact role of antiplatelet treatment in this group of patients.

These three major overviews of the use of antiplatelet treatment in various groups of patients provide valuable information on which to base clinical practice; they also highlight topics requiring further investigation. Patients with established atherosclerosis (affecting their cardiac, cerebral, or peripheral arteries) benefit in terms of fewer subsequent vascular events. Patients undergoing revascularisation procedures (coronary grafting, peripheral grafting, and angio-

plasty) also benefit in terms of better patency of the vessel and fewer vascular events unrelated to the procedure. The role of antiplatelet treatment in prophylaxis against venous thromboembolism is less certain as other effective treatment (subcutaneous heparin) exists.¹⁶

In all groups of patients aspirin, at a dose of 75-325 mg, seems as effective as any other single agent or combination of agents. The duration of treatment still needs to be determined, but for those with established atherosclerosis lifelong treatment may be indicated. For patients without clinically apparent atherosclerotic disease the potential haemorrhagic complications of routine use of aspirin may outweigh its benefit.

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Who benefits from medical interventions?

Treating low risk patients can be a high risk strategy

The results of clinical trials are often expressed in relative terms—for example, a particular treatment reduces the risk of an adverse outcome by 40%. Yet knowing that the treatment reduces the risk of such an outcome from 5% to 3% (an absolute reduction of 2%) may be more useful clinically.¹

The effects of antiplatelet treatment are a case in point. The meta-analysis of randomised controlled trials of such treatments by the Antiplatelet Trialists' Collaboration shows that the risk of dying from a vascular cause varies substantially according to patient group (p 81).² It ranges from 10% over one month for patients with an acute myocardial infarction at entry to the trial, through 9% over two years for those who had survived an acute myocardial infarction, down to only 2% over five years in trials of primary prevention.

With such varying risks of future vascular events it is unsurprising that the absolute effects of antiplatelet agents differ substantially by patient group. Reductions in relative risks may be similar—antiplatelet drugs reduce the risk of future non-fatal myocardial infarction by 30% in trials of both primary and secondary prevention. But when the results are presented as the number of patients who need to be treated for one non-fatal myocardial infarction to be avoided they look very different.

In secondary prevention 50 patients need to be treated for two years, while in primary prevention 200 patients need to be treated for five years, for one non-fatal myocardial infarction to be prevented. In other words, it takes 100 patient-years of treatment in secondary prevention or 1000 patient-years of treatment in primary prevention to produce the same beneficial outcome of one fewer non-fatal myocardial infarction.

The fact that the risk that patients are at before they begin treatment affects their absolute benefits from treatment has been much discussed with regard to the treatment of hypertension.^{3,5} In randomised controlled trials treatment has consistently reduced the risk of stroke by 40% (expressed in relative terms).⁶ The 10-fold variation in stroke rates in patients in these trials, however, leads to the number of patient-years required to prevent one stroke ranging from around 100 to 1000. To prevent one vascular death the equivalent figures are about double these. The baseline characteristics of patients—age, sex, blood pressure, other risk factors for cardiovascular disease, and end organ damage—can discriminate groups with widely differing risks of stroke and coronary heart disease. The balance between the benefits and side effects of treatment will be more

favourable among patients at a higher risk of vascular disease.

Consider, for example, the systolic hypertension in the elderly programme (SHEP), in which 28% of the treatment group reported what they considered to be an "intolerable problem" during treatment, a significantly higher proportion than the 21% recording such an event in the placebo group.⁷ The trade off between reducing the risk of a stroke or vascular death and the increase—affecting 7 of every 100 patients—in the risk of experiencing an "intolerable problem" would clearly be weighed differently by patients at different levels of cardiovascular risk.

This balance between the benefits and unwanted side effects of treatment is particularly stark when such side effects are serious. The balance will be more favourable for those patients with a higher risk of the condition that the treatment aims to prevent. For antiplatelet agents, some evidence exists that they may slightly increase the risk of haemorrhagic stroke. For participants in primary prevention trials who are at low risk this contributes to the fact that the reductions in vascular death in the treatment arms of these trials are small and non-significant, translating into a best estimate of 1 death avoided for each 1450 person-years of treatment. This compares unfavourably with one vascular death avoided for each 75 person-years of treatment in the survivors of a myocardial infarction and one death avoided for each 3 person-years of treatment in patients treated during an acute myocardial infarction.

Similar considerations apply to the appropriate use of cholesterol lowering drugs.⁸ For patients at a high risk of dying from coronary heart disease, reducing blood cholesterol concentrations with drugs reduces mortality. For patients at a lower risk—for example, those with moderately high cholesterol concentrations but without symptomatic cardiovascular disease—cholesterol lowering drugs may have increased the risk of death. For such patients a small absolute increase in the risk of death attributable to treatment, of around 1-2 deaths per 1000 patient-years of treatment, is enough to cancel out any treatment related fall in the risk of coronary heart disease.

Small risks may outweigh small benefits

Commenting on this phenomenon, Geoffrey Rose pointed out that "in mass prevention, each individual has usually only a small expectation of benefit, and this small benefit can easily be outweighed by a small risk."⁹ This should serve to caution against the widespread use of drugs to prevent disease until overall benefits have been established by controlled trials.¹⁰

A final example from cardiovascular medicine concerns angiotensin converting enzyme inhibitors for treating and preventing heart failure. While the use of these drugs in acute myocardial infarction apparently produces only small benefits,¹¹ their long term use in patients with, or at risk of developing, heart failure has produced more impressive results. The results of five large trials,¹²⁻¹⁶ presented in the figure, show that treating patients at high risk produces considerably greater benefit than treating patients at lower risk. With the range in the number of patients who need to be treated for a year for one death to be prevented varying from 2 to 330, depending on their risk of death due to existing cardiac disease, evaluations of risk-benefit and cost-effectiveness will vary greatly among different clinical situations.

Outside cardiovascular medicine, the same relation is evident—for example, when the benefit of treating HIV infection with zidovudine is assessed. The first big trial in patients with AIDS or AIDS related complex at high risk of death reported impressive effects: 42 fewer deaths per 100 person-years of treatment.¹⁷ Yet in patients with less advanced

Effect of angiotensin converting enzyme inhibitors on mortality in patients with ventricular dysfunction: results from five controlled trials

HIV infection entered into the large Concorde trial, early use of zidovudine was associated with a non-significant adverse effect on mortality.¹⁸ When the relation between the benefit of treatment and mortality among the controls in six published trials is examined,¹⁷⁻²² increasing risk of death with controls is associated with an increase in the numbers of deaths delayed by zidovudine treatment. For people with asymptomatic HIV infection the side effects of zidovudine together with the uncertain effects on mortality may make treatment an unattractive option. A recent formal demonstration that zidovudine treatment early in the course of disease is not cost effective supports this conclusion.²³

The greater benefit (and reduced likelihood of harm) experienced by patients at higher risk has several implications for clinical practice and public health policy. Firstly, how trial data are presented may influence doctors' perceptions of the advisability of treatment. Converting relative measures of benefit into measures such as the number of patients who need to be treated to prevent one outcome event can modify the response of doctors to the results of trials, arguably in the right direction.²⁴ Both investigators and pharmaceutical companies should be encouraged to provide absolute as well as relative measures of benefit produced by treatment.

Secondly, clinical guidelines should reflect the association between degree of benefit and level of risk. This does not necessarily occur, as the first set of guidelines from the United States national cholesterol education program shows.²⁵ These recommended intensive treatment for some groups of patients who were at a considerably lower risk of a coronary event than other groups of patients who were deemed not to require any special attention.²⁶ Encouragingly, both the recent revision of these guidelines²⁷ and a new set of recommendations for treating raised blood pressure from New Zealand²⁸ have taken a more risk based approach

to decisions on treatment. Thirdly, meta-analyses should incorporate estimates of the risk in the included trials to examine whether systematic differences in benefit are seen in relation to the degree of risk of participants in the trials.⁸ Finally, since those who gain the most from medical treatment are those who have most to gain, the irrationality of current suggestions that population groups at increased risk of disease—such as smokers—should not be treated should be recognised.

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IgA nephropathy

The commonest form of glomerulonephritis in industrialised countries

Since idiopathic IgA nephropathy was first reported a quarter of a century ago it has evolved from being a curiosity to becoming the commonest form of glomerulonephritis in industrialised countries. A recent international meeting held to mark the 25 years of study of IgA nephropathy concentrated on its aetiology and pathogenesis but had also to acknowledge that nephrologists still do not know how to treat the disease.¹

Clinical observation over two decades has shown that spontaneous remission may occur but that 15-20% of patients develop end stage renal failure within 10 years of diagnosis. The risk factors for progression are impaired renal function at presentation, heavy proteinuria, hypertension, and (curiously) absence of the typical symptom—recurrent macroscopic haematuria. The systemic nature of IgA nephropathy is shown convincingly by its recurrence in patients who receive a kidney transplant and, more remarkably, by the disappearance of IgA deposits when a kidney from someone with the disease is inadvertently transplanted into someone with renal failure from another cause.

When IgA nephropathy was first described, IgA itself—and the fact that it was produced by mucosal cells—had been discovered only a few years earlier. The deposition of this immunoglobulin in glomeruli was explained as an immune

complex disease in which an antigen or antigens came into contact with the mucosa and induced an IgA antibody response. This led to antigen-antibody complexes circulating and being deposited in the kidneys. In some patients the serum IgA has an increased antibody activity against food antigens such as gliadin and casein and the amount of circulating complexes is increased, but these are not consistent findings. Nor is there good evidence that the mucosal surfaces are incompetent at one of their normal tasks—preventing antigen or antigen-antibody complexes from entering the circulation. As with any disease of unknown cause that is mediated by the immune system, autoimmunity was invoked. Some support came from the finding that in some patients serum IgA is bound to fibronectin or collagen, both of which are normal constituents of glomeruli; but this binding was later shown not to be an antigen-antibody combination.

Meanwhile, the physiology and structure of IgA became better understood. It may still be insufficiently known that bone marrow, which produces immunoglobulins, accounts for one third of normal production of IgA. Patients with IgA nephropathy produce excess amounts of IgA in their bone marrow²—an observation that underlines the systemic nature of IgA nephropathy. B cells in the tonsils have also been