# Letters

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## Taking precautions with angiotensin converting enzyme inhibitors

### Angiotensin converting enzyme inhibitors are not proved to cause loss of renal mass

EDITOR—We agree with Kumar et al that an awareness of the high risk of atherosclerotic renal artery stenosis is important in patients with vascular disease elsewhere, particularly if treatment with angiotensin converting enzyme inhibitors is being considered.[1] We strongly disagree with the suggestion, however, that high risk patients starting treatment with angiotensin converting enzyme inhibitors should first be screened for unilateral renal artery stenosis, for two reasons.

Firstly, the assertion that angiotensin converting enzyme inhibitors cause loss of renal mass is unproved. Irreversible structural damage to kidneys with renal artery stenosis may result from hypertensive nephrosclerosis, cholesterol embolisation, ischaemia as a result of tight renal artery stenosis, and, ultimately, total occlusion.[2] Angiotensin converting enzyme inhibitors cause an acute decrease in glomerular filtration rate, but in cases where this proves irreversible, the likeliest explanation is progression of the underlying disease. Renal blood flow is not specifically reduced by angiotensin converting enzyme inhibitors,[3] although any drug that lowers blood pressure might reduce renal blood flow in the presence of clinically important renal artery stenosis.[4] If screening for unilateral atherosclerotic renal artery stenosis were important, it would therefore be important for all high risk patients, not only those prescribed angiotensin converting enzyme inhibitors.

Secondly, however, we do not believe that screening for unilateral atherosclerotic renal artery stenosis is worth while. The rationale for screening would presumably be to prevent end stage renal failure secondary to bilateral renal artery occlusion. Evidence is lacking that percutaneous angioplasty, with or without stenting, prevents end stage renal failure in unilateral atherosclerotic renal artery stenosis.[5]

Although unilateral atherosclerotic renal artery stenosis is common and easy to find in high risk patients, current evidence does not tell us how to manage it once it is found.

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### Screening for unilateral renal artery stenosis cannot be justified

EDITOR—The editorial by Kumar et al reminds us that treatment with angiotensin converting enzyme inhibitors can cause harm in patients with unilateral or bilateral renal artery stenosis.[1] Their suggestion, however, that patients at high risk should undergo screening with duplex ultrasonography is impracticable and would restrict its use in those for whom there is proved benefit.

Kumar et al's definition of high risk includes most patients who are currently being treated with angiotensin converting enzyme inhibitors—elderly people with hypertension, and patients with diabetes or coronary heart disease. Implementing the recommendations of Kumar et al would have substantial clinical and financial implications. Duplex ultrasonography requires considerable technical skill, is not available in every centre, and is not currently thought to be sufficiently sensitive to be an effective screening method,[2] even in patients with a technically adequate scan. Most patients with heart failure and almost all other patients have started treatment with angiotensin converting enzyme inhibitors in the community. What are the implications, therefore, for general practitioners without easy access to screening facilities?

Evidence from multiple randomised clinical trials shows that it is neither necessary nor possible to screen these patients. In the evaluation of losartan in the elderly study, treatment with either losartan or captopril was associated with only a 10.5% incidence of renal dysfunction, defined as a rise in serum creatinine of 26.5 µmol/l, despite patients' advanced years (two thirds of patients aged over 70) and high incidence of diabetes (25%), hypertension (57%), and previous myocardial infarction (50%).[3] Data from the fourth international study of infarct survival show that early oral treatment with angiotensin converting enzyme inhibitors after myocardial infarction was safe and associated with an additional 1.5 lives saved per 1000 patients treated within the first 24 hours.[4] Screening this unstable population would be impossible. All these patients have coronary artery disease, and many have concomitant diabetes mellitus or peripheral vascular disease.

There is no evidence that angiotensin converting enzyme inhibitors are detrimental in unilateral renal artery stenosis. In a recent study of elderly patients with heart failure, many of whom had unilateral renal artery stenosis, angiotensin converting enzyme inhibitors were tolerated excellently.[5] Furthermore, no evidence exists that relief of unilateral stenosis is associated with an improved outlook. What is, therefore, to be done with patients with unilateral stenosis? Are they to be denied the proved benefits of angiotensin converting enzyme inhibitors in the absence of evidence of harm? Kumar et al have not fully considered the implications of their recommendations. Currently, screening for unilateral renal artery stenosis cannot be justified.

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1 Kumar A, Asim M, Davison AM. Taking precautions with ACE inhibitors. *BMJ* 1988;316:1921. (27 June.)
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5 MacDowall P, Kalra PA, O'Donoghue DJ, Waldek S, Mamtora H, Brown K. Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet* 1998;352:13-6.

### Clinically significant deterioration in renal function occurs rarely

EDITOR—Kumar et al urge caution in the increasingly widespread use of angiotensin converting enzyme inhibitors.[1] This is a timely reminder that these drugs can cause problems in certain patients. They are now regarded as first line antihypertensive treatment in patients with diabetes, particularly if they have proteinuria.[2] It is widely accepted that renal ultrasonography should be done in all patients with diabetes who have persistent proteinuria, in order to ensure that this has no non-diabetic cause. Asymmetrical renal size discovered this way can lead to the suspicion of unilateral renal artery stenosis. In addition, Doppler ultrasonography of the renal arteries, as suggested by Kumar et al, could also be done in these patients.

In view of the theoretical risk of clinically important unilateral renal artery disease, Kumar et al say that screening for renal artery stenosis is also required in all patients with diabetes, people aged over 50 with hypertension, and patients with coronary artery or peripheral vascular disease. This may not only lead to a considerable increase in cost for screening a large number of patients, but also provide a further reason to delay giving treatment that preserves cardiac and renal function to those most in need of it.

To ascertain whether angiotensin converting enzyme inhibitors have caused deterioration in renal function in patients at very high risk of renovascular disease, I have reviewed 20 patients with non-insulin dependent diabetes who have peripheral vascular disease (loss of dorsalis pedis and posterior tibial pulses in one or both feet, plus symptoms of claudication), who started treatment with angiotensin converting enzyme inhibitors at least 12 months previously for hypertension. None of these patients showed an acute deterioration in renal function. Evidence for this is a significant rise in serum creatinine (96 (SD 17) mmol/l before treatment, 93 (SD 23) mmol/l one year after treatment, $P = 0.672$ (paired $t$ test)). Furthermore, only one patient had clinically important asymmetry ($>10\%$) in right and left renal function on radionuclide renography using diethylenetriaminepenta-acetic acid labelled with technicium-99m.

Although unilateral renal artery stenosis is common among the patient groups that Kumar et al recommend we screen, and a theoretical risk of acute deterioration in renal function exists, in practice a clinically important deterioration in renal function occurs rarely, even in a group of patients at very high risk of renal arterial disease.

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2 Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329:1456-62.

### Funding for large scale screening is not available

EDITOR—Although we do not know whether treatment with angiotensin converting enzyme inhibitors hastens the loss of renal function in the long term when given to people with unsuspected unilateral renovascular disease, Kumar et al say that it might be wise to screen anyone at high risk with duplex or colour Doppler ultrasonography.[1]

The implications of this are far reaching. In my practice of 10 000 patients, 250 people over the age of 50 are prescribed angiotensin converting enzyme inhibitors. In this district, an estimated 2000 people would need screening each year and, assuming that 5% of these had clinically important renovascular disease, 100 would need a stent. The funding to do this on such a large scale does not exist, and I believe that we need more evidence than Kumar et al have provided either to divert the money from other, more proved uses or to restrict the use of angiotensin converting enzyme inhibitors. More information is needed before we alter clinical practice, which would probably mean using alternative drugs.

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1 Kumar A, Asim M, Davison AM. Taking precautions with ACE inhibitors. *BMJ* 1998;316;1921. (27 June.)

### Authors' reply

EDITOR—We wanted to increase awareness of the potential risks associated with the use of angiotensin converting enzyme inhibitors in patients with unsuspected atherosclerotic renal artery disease, prompted by the admission of several elderly patients with acute renal failure in whom renal function, as assessed by serum creatinine concentration, had not been checked before or after starting treatment with these drugs. Although such inhibition in the presence of bilateral renal artery stenosis is likely to be harmful, recent findings suggest that unilateral stenosis may be equally important.[1] In some patients renal function in the kidney affected by stenosis is better than in the contralateral kidney with a normal artery.[1] The kidney with the stenotic arterial lesion may thus be protected, at least in part, from the deleterious effects of hypertension and atheroembolic disease to which the other kidney is exposed. Injudicious use of an angiotensin converting enzyme inhibitor might lead to irreversible injury to the kidney that may be contributing most of a person's glomerular filtration.

Louden and Main assert that any drug that lowers blood pressure might reduce renal blood flow in the presence of clinically important stenosis of the renal artery. Angiotensin converting enzyme inhibitors pose a greater hazard; in patients with hypertension due to unilateral atheromatous stenosis of the renal artery, the glomerular filtration rate in the stenotic kidney decreased markedly after inhibition of angiotensin converting enzyme, whereas it decreased only slightly with a calcium antagonist.[2] Dependency on angiotensin II for the residual function in a kidney with stenosis of the artery, and a further decline in glomerular filtration after using these inhibitors, form the basis for angiotensin converting enzyme inhibitor renography as a diagnostic tool in unilateral arterial disease.[3]

Studies examining the efficacy and safety of angiotensin converting enzyme inhibitors and angiotensin II antagonists in treating heart failure in elderly people have shown that the prevalence of atherosclerotic renovascular disease in these patients is much greater than had been recognised previously.[4 5] Murdoch suggests that a 10.5% incidence of renal dysfunction in patients taking these drugs in the evaluation of losartan in the elderly study[4] is acceptable, but nephrologists find this approach alarming. How many of these patients would have developed progressive renal impairment had their renal function not been monitored as assiduously as happens during drug trials?

For elderly patients, particularly those with comorbid vascular diseases, the diagnosis of occult atherosclerotic renal artery stenosis is desirable, and careful monitoring of renal function essential in those for whom treatment with angiotensin converting enzyme inhibitors is being considered. The costs of screening for renal artery stenosis are far lower than the suffering and expense of kidney dialysis.

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## Clinicians should be proactive in testing for asthma

EDITOR—Britton and Lewis adopt a nihilistic position in saying that tests for asthma are of little value and that diagnosis should be based on clinical criteria.[1] The symptoms of asthma are non-specific, which is why so many of the patients that we see in our clinics with a diagnosis of asthma turn out not to have the disease and are being treated inappropriately.

Asthma is a well defined disease characterised by variable airflow obstruction, airway hyperresponsiveness, and eosinophilic mucosal inflammation which is caused, in most cases, by an aberrant immune response to inhaled allergens.[2] We would therefore take the opposite position

to Britton and Lewis and say that clinicians should be much more proactive in supporting a clinical suspicion of asthma with objective testing. We believe this should routinely include formal reversibility studies (home peak flow readings are insensitive, non-specific, and have limited value in making a diagnosis[3 4]), measurement of airway responsiveness, and assessment of airway inflammation, particularly using induced sputum to detect airway eosinophilia.[5] Only in this way can clinicians distinguish between asthma and the many other conditions that have a similar clinical presentation. Diagnosing asthma on clinical grounds alone is like diagnosing colitis from a change of bowel habit or the cause of a fever by feeling the patient's brow.

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1 Britton J, Lewis S. Objective measures and the diagnosis of asthma. *BMJ* 1998;317:227-8. (25 July.)
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## Methods used for suicide vary between regions in the developing world

Editor—Eddleston et al point out that deliberate self harm and suicide are serious public health problems in developing countries.[1] We agree with their suggestions aimed at reducing the mortality associated with organophosphorus and pesticide poisonings, but it is important to note the considerable variation in the methods used for suicide between regions in the developing world, and even greater variations between people attempting and completing suicide.

In India self immolation and hanging remain the commonest methods for completed suicides, whereas poisoning is a common form of deliberate self harm. In Goa (a maritime state) drowning is another common method of suicide. The populations at risk also vary; for example, although most people who attempted suicide in Eddleston et al's report were under 30, most who complete are older. Social stressors may vary as well: in Sri Lanka the civil war is an important stressor, whereas in Goa problem drinking by male relatives, harassment of women by in-laws and husbands, and loneliness due to migration of children are important.[2]

While discussing prevention of deliberate self harm, the authors do not deal adequately with the recognition and management of common mental disorders, such as depression in general and primary healthcare settings. Studies from south Asia show that up to half of all adult primary care attenders have a clinically important emotional disorder, most of which go undetected and treated with many drugs.[2 3] In a recent study from India 18% of all adult attenders admitted to suicidal ideas in the week before interview but under a fifth had discussed these with their doctor.[2]

Public health initiatives to meet this challenge should include raising awareness in the community and among policymakers in the government and health funding agencies of the risks and treatments for depression and anxiety; training health workers in general and primary healthcare settings in communication skills and the recognition and appropriate management strategies of emotional disorders; setting up multidisciplinary teams to provide interventions at the community level; integrating mental health in the work of non-governmental organisations, which are playing an increasingly important part in providing health care in many developing countries; and closer research and service links between departments of psychiatry and community medicine.

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## Association between birth weight and death from heart disease

### Data do not support association

Editor—Leon et al claim that their study is "the most persuasive evidence of a real association between size at birth and mortality from ischaemic heart disease."[1] However, the study is open to different interpretations and, in my view, inflicts a serious wound on the birth measurement and adult disease hypothesis.

Their table 3 shows that there was no significant association between birth weight and all cause mortality in either sex. Both sexes showed a positive association between birth weight and death from neoplasms and respiratory disease, though none of these were significant. The negative association between birth weight and deaths from circulatory disease was significant only in men. In women there were no significant associations between birth weight and any cause of death. Subsequently, most of the analysis concentrates on the association of death from ischaemic disease and birth measurements in men.

This study is claimed (probably correctly) to have unique features. It certainly has large numbers of deaths to analyse. Yet no significant association was found in women, and that in men, with ischaemic heart disease, was presumably compensated for by other causes of death, which made the association with all cause mortality non-significant. Thus, of all the possible associations with birth weight, and despite the large number of deaths, only the association between birth weight and death from ischaemic heart disease in men remains significant. I do not see how these data justify the key message "adult mortality from ischaemic disease increases as size at birth declines."

There is also the question of socioeconomic confounding. Leon et al state that adjustment for socioeconomic circumstances produced only a small reduction in the strength of the association between birth weight and mortality from ischaemic heart disease. The problem of adjusting for socioeconomic factors in this context has been much debated. In this paper the adjustment brought the upper limit of the confidence intervals perilously near unity. If the precision of this measurement matched that of the others, even the single significant result might be in peril.

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1 Leon DA, O Lithell H, Vâgerö D, Koupilová I, Mohsen R, Berglund L, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915-29. *BMJ* 1998;317:241-5. (25 July.)

### Authors' reply

Editor—Jarrett draws attention to the intriguing positive association between birth weight and neoplasms that we observed. Interest is growing in whether risk of certain cancers is increased in individuals who are large at birth.[1] If true, this may indeed partly compensate for the negative effect of reduced size at birth on later mortality from circulatory disease. However, it is precisely the specificity[2] of the negative association of size at birth with mortality from ischaemic heart disease that strengthens the case for this association having a causal element. Although not reaching significance, a similar association was observed in women, with risk of death from ischaemic heart disease falling with increased size at birth. We therefore stand by our assertion that risk of death from ischaemic heart disease increases as size at birth falls.

The question of socioeconomic confounding is an important one that we addressed. Jarrett is wrong to focus on confidence intervals. The main criterion for judging the extent to which there may be inadequate adjustment for a confounder is the magnitude of the change in the estimates of effect, rather than changes in the P values or width of confidence intervals. In our case the rate ratio for ischaemic heart disease associated with a 1 kg increase in birth weight was 0.77 in the crude data and 0.82 when adjusted for socioeconomic characteristics at the birth of the subject and at two points in adult life. We believe that this shows that although a small fraction of the crude association between size at birth and ischaemic heart disease is attributable to

socioeconomic confounding, there remains a consistent and robust effect that is not.

The evidence for impaired fetal growth being associated with ischaemic heart disease in men is steadily accumulating. Unlike other studies, ours has largely been able to exclude the role of bias and confounding. Further epidemiological studies in other populations are desirable, particularly concerning the association in women and the potential modifying effects of factors such as obesity in adult life. However, the understandable scepticism about the reality of these associations that prevailed when the fetal origins hypothesis was first put forward some years ago should now give way to critical thinking and investigation of plausible underlying mechanisms. Among many other questions that need to be addressed is the extent to which maternal nutritional status drives this association.

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## Should industry sponsor research?

### Researchers must recognise damage done by overt association with formula manufacturers

Editor—The issue that Lucas fails to tackle in his article on collaborative research with infant formula companies is conflict of interest in relation to research.[1] Much of his article justifies the need for bottle feeding (with which no one would argue), plays up the educational role of formula manufacturers (highly questionable, as their material has been shown to have biased content), and casts doubt on the long term benefits of breast feeding (not relevant to the key issue). He strays into the area of educational sponsorship, where there is far less justification for industry support than in research, which is notoriously difficult to fund.

Lucas makes virtually no mention of what the opponents of sponsorship are worried about: the aggressive sales tactics of formula manufacturers in poor developing countries (now confirmed in a global study that has been endorsed by Unicef[2]) and the inevitability of a bias towards formula feeding in those who take money from the industry. It is a blot on the reputation of paediatricians world wide that they have been seen to side with milk companies in what is a highly unbalanced marketing struggle; the example of the Indian Paediatric Association is a shining exception.

For most babies who need artificial milk, the present formulas serve them well and no further modification seems necessary. Perhaps a compromise approach is possible for the small number of research centres working on new preterm formulas. Could a formula company's funds be channelled through an independent organisation and the company remain anonymous? It is essential not only that there is no conflict of interest but that researchers are seen to recognise the damage that can be done internationally by overt association between paediatricians and formula manufacturers.

We hope that the new sponsorship policy being worked on by the Royal College of Paediatrics and Child Health will clarify these issues and take a strong stand for breast feeding.

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2 Taylor A. Violations of the international code of marketing of breast milk substitutes: prevalence in four countries. *BMJ* 1998;316:1117-9. (11 April.)

### Funding of research by infant formula companies

Editor—The funding of research by infant formula companies is necessary, unavoidable, and beneficial.[1] Despite the importance of nutrition in medicine and the depth of understanding of nutritional processes on a molecular level, funding for nutritional research is difficult to obtain in competition with funding for molecular biology. Applied nutritional research is anyway most appropriately funded by industry. The scientific staff of infant formula companies bring extensive expertise to nutritional research collaboration.

The ethical debate on this subject was informed by Lucas, whose most celebrated research was supported by infant formula companies. Among his many conclusions was the fact that breast milk has vital benefits in the nutrition of low birthweight infants.[2] The counter argument was posed by Rundall, whose organisation, Baby Milk Action, is engaged in advocacy and lobbying rather than nutritional research.[3] This follows an outdated publication on the infant formula code.[4] Wise, commenting on this report, is forced to speculate that academic nutritionists prepared to communicate their opposition to research support by the infant formula industry could not be found.

In the same issue of the *BMJ* Smith, in a constructively worded editorial, discusses the importance of disclosure of conflict of interest.[5] Lucas's article clearly identifies his position. The position of Rundall is more opaque, perhaps because the past 10 years of her high profile campaign against the infant food industry might, in some readers' minds, have disqualified her as an objective commentator.

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1 Lucas A. Ethical debate: Should industry sponsor research? Collaborative research with infant formula companies should not always be censored. *BMJ* 1998;317: 337-8. (1 August.)
2 Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. *Lancet* 1990;336:1519-23.
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### Positive messages on breast feeding would result in need for infant formula decreasing

Editor—It is sad that such an eminent nutritionist as Lucas should seek to be an apologist for the infant food industry in supporting their efforts to sponsor medical research.[1] This is especially poignant in view of the fact that Lucas himself has provided valuable evidence of the beneficial effects of breast feeding on later intelligence and is well aware of the other major benefits that accrue from breast milk.

I am disturbed to read that Lucas considers that manufacturers have a "major role in the health care of infants." I agree that there is an obligation for them to ensure that feeding their products to infants has no adverse consequences, especially in view of the known benefits of breast milk. But it is more likely that their main research thrust will be towards making their products more and more similar to breast milk—an increasingly expensive exercise.

The Medical Research Council unit in which Lucas works is funded independently, which gives it more credence. Most paediatricians in the United Kingdom support his views on sponsorship, which shows a lukewarm attitude towards breast feeding. The Indian Paediatric Association has cut itself off from industry funding, and many doctors in the United Kingdom would like the Royal College of Paediatrics and Child Health to do the same. It would be of great benefit to the long term health of the United Kingdom if distinguished scientists like Lucas concentrated on transmitting positive messages on breast feeding in an effort to increase the rate and duration of breast

feeding. The amount of infant formula needed would then decrease and the role of the industry would be confined to the margins where it belongs.

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1 Lucas A. Ethical debate: Should industry sponsor research? Collaborative research with infant formula companies should not always be censored. *BMJ* 1998;317: 337-8. (1 August.)

### Portman Group has always openly acknowledged its source of funding

EDITOR—Far from being a "front organisation" for the drinks industry, as alleged by Edwards,[1] the Portman Group has always been open in acknowledging that it is funded by the leading drinks producers. It must surely be right that these companies play their part, alongside parents, health professionals, and others, in promoting sensible drinking and helping to prevent alcohol misuse. Our work is carried out irrespective of the commercial consequences to the industry, as those companies that have been forced to spend considerable sums of money on modifying or scrapping drinks whose name and packaging failed to meet our standards of social responsibility in marketing could testify. Edwards is well short of the mark in accusing the drinks industry of using the tactics of the tobacco industry. Those who produce and sell alcohol have no need to resort to such tactics. A vast body of research shows that alcohol in moderation is perfectly compatible with a healthy lifestyle for most people. Edwards is notably isolated in his reluctance to accept the overwhelming consensus of scientific, academic, medical, and health promotion opinion that informed and supports the government's balanced guidelines on sensible drinking.

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1 Edwards G. Ethical debate: Should industry sponsor research? If the drinks industry does not clean up its act, pariah status is inevitable. *BMJ* 1998;317:336. (1 August.)

## Rescue thrombolysis for failure of primary thrombolysis cannot be justified

EDITOR—Drenth et al suggest a policy of repeat thrombolysis if initial thrombolysis fails,[1] but their arguments are flawed.

Firstly, they state that a routine policy of rescue angioplasty cannot be justified from a review of the literature, although they fail to mention that the trial by Ellis et al showed a significant reduction in the incidence of death or severe heart failure in the rescue angioplasty group compared with the conservative group.[2]

Secondly, there are far fewer published data from randomised trials comparing the use of rescue thrombolysis with conservative treatment, yet the authors claim that these data support their current practice. Only one trial randomising 37 patients has compared rescue thrombolysis with conservative treatment, and benefit in the rescue thrombolysis group was confined to a subgroup of patients in whom initial thrombolysis had failed to achieve a systemic lytic state (fibrinogen concentration $>1$ g/l).[3] Drenth et al do not state whether fibrinogen concentrations were measured in their patients.

Thirdly, the 51 patients they describe were not randomised to either rescue angioplasty or rescue thrombolysis; the choice was left to the attending doctor, with the potential for considerable bias in the assignment of treatment strategy. In addition, given that roughly half of all patients fail to respond within 90 minutes to initial thrombolytic treatment, the small number of patients recruited in a four year period points to, at worst, a high degree of selection bias or, at best, minimal exposure to patients with acute myocardial infarction. This number of patients is also too small to allow such a decisive statement about the rates of major bleeding in each group.

Fourthly, the authors state that the extent of myocardial infarction was lower in the rescue thrombolysis group, as evidenced by lower mean maximal creatinine kinase concentrations. The more likely explanation for this finding, however, is the earlier restoration of coronary arterial flow achieved by rescue angioplasty, with subsequent earlier washout of high creatinine kinase concentrations.

The management of failed thrombolysis is controversial. An optimal management strategy is likely to be provided only by multicentre, prospective randomised trials comparing all therapeutic options. Retrospective analysis of small, non-randomised studies, the design of which may reflect the personal beliefs of individual doctors, should be interpreted with caution.

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1 Drenth JPH, Uppelschoten A, Hooghoudt THE, Lamfers EJP. Rescue thrombolysis may work even though primary thrombolysis has failed. *BMJ* 1998;317:147. (11 July.)
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## Chiropractic for low back pain

### Experts in both UK and US believe that chiropractic works

EDITOR—Ernst and Assendelft's editorial on chiropractic for low back pain seems to have been written more in a spirit of professional aversion than in one of critical doubt.[1] This impression is conditioned by previous commentaries by these authors in the popular press and the biomedical literature.

The question is, why? There is substantial scientific evidence that the manipulation that chiropractors (and indeed osteopaths and some physiotherapists) do for back pain is both effective and safe. This evidence has been reviewed by multidisciplinary panels of experts in both the United Kingdom and the United States, which has resulted in the production of two national clinical practice guidelines for acute back pain that totally disagree with these authors. The only randomised controlled trial of overall chiropractic management for back pain,[2 3] in contrast to manipulation alone, is not mentioned in this editorial. Yet this trial (included erroneously by one of these authors in 1991 in a review of manipulation trials) was ranked as high quality, was positive in its evidence for chiropractic management, and yet was subsequently condemned as seriously flawed by Ernst in a separate paper. This editorial is equally contradictory.

No one would dispute the need to research further the evidence for the effectiveness, cost effectiveness, and safety of manipulation and associated treatment approaches. The Medical Research Council is currently supporting a large randomised trial by a multidisciplinary research team led by the department of health sciences and clinical evaluation at the University of York. Many other studies are in progress. Nevertheless, the United Kingdom's current national clinical practice guideline and evidence review states: "Within the first 6 weeks of acute or recurrent low back pain, manipulation provides better short-term improvement in pain and activity levels and higher patient satisfaction than the treatments to which it has been compared" and "the risks of manipulation for low back pain are very low, provided patients are selected and assessed properly and it is carried out by a trained therapist or practitioner."[4]

The Chiropractors and the Osteopaths Acts and the chiropractors' and the osteopaths' general councils will provide these assurances for the public, but there is no certainty in science. Those who demand certain proof of things are already prejudiced against them.

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### Efficacy of spinal manipulation for low back pain has not been reliably shown

EDITOR—In their editorial[1] Ernst and Assendelft refer to a review by Shekelle et al, which concludes that "spinal manipulation is of short-term benefit in some patients, particularly those with uncomplicated, acute low-back pain."[2] Ernst and Assendelft point out that this work did not contain a single trial of chiropractic. The references in the review by

Shekelle et al do in fact include chiropractic trials.[2] The second reference listed is the trial by Meade et al.[3]

The second paragraph of the editorial refers to a review by Assendelft et al of eight randomised controlled trials of chiropractic treatment. This review concludes that the eight trials provide no convincing evidence for the effectiveness of chiropractic treatment for acute or chronic low back pain.[4] Therefore, readers are left with the impression that chiropractic treatment is less effective than manipulation in general. Had the authors included a seventh reference to their own work—a review of spinal manipulation for low back pain[5] published in the same year as the review of the chiropractic trials—it would have changed readers' impression altogether. This document reviews 36 randomised clinical trials comparing manipulation with other treatments and concludes that "the efficacy of spinal manipulation for patients with acute or chronic low back pain has not been demonstrated with sound randomised clinical trials."[5]

These inaccuracies show that one can never be too critical when reading published material.

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1 Ernst E, Assendelft WJJ. Chiropractic for low back pain. *BMJ* 1998;317:160. (18 July.)
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### Chiropractic is one of safest forms of treatment available

Editor—If you would like information on chiropractic's track record for treating low back pain[1] perhaps you should ask the 20 million patients who will visit doctors of chiropractic this year alone. Patients' satisfaction with chiropractic care has consistently rated higher than traditional medical care for low back pain. A recent study found that "compared to those who sought care from medical doctors, those who sought care from chiropractors were more likely to feel that treatment was helpful, more likely to be satisfied with their care, and less likely to seek care from another provider for that same episode of pain."[2]

Shekelle et al showed that chiropractic treatment is appropriate for low back pain in a considerable number of cases. They found that 46% of a sample of patients with low back pain received appropriate care from doctors of chiropractic—an appropriateness rating similar to that of common medical procedures.[3]

Chiropractic is one of the safest forms of treatment available today. According to a study by Hurwitz et al, a serious adverse reaction from cervical manipulation occurs once in 1 million manipulations.[4] Complication rates for manipulation of the lumbar region of the spine are even lower. When compared with the number of illnesses and deaths that will occur this year from the appropriate use of prescription and over the counter drugs, the number of serious complications from chiropractic treatment is extremely low. A study by Lazarou et al found that more than 2 million Americans become seriously ill every year from reactions to correctly prescribed drugs and 106 000 die from those side effects.[5]

My profession, like every other healthcare profession, is by no means beyond reproach. I agree that more and better chiropractic research is required. More and better medical research is required as well. I hope that the chiropractic and medical professions will continue to work together in this regard. Our patients will be the ultimate beneficiaries.

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### Evidence for manipulation is stronger than that for most orthodox medical treatments

Editor—As one of the coauthors of the Clinical Standards Advisory Group's report on back pain[1] and the Royal College of General Practitioners' guidelines on acute low back pain,[2] I am disappointed by Ernst and Assendelft's editorial on chiropractic.[3] The authors present a critical view of chiropractic under the guise of scientific objectivity, but I had hoped that we had got beyond that stage of interprofessional confrontation.

Burton and I recently reviewed international guidelines for low back pain, and none of them specifically recommend chiropractic.[4] What they do all say, and what all recent reviews conclude to varying degrees, is that considerable evidence now exists that manipulation is an effective treatment for low back pain. Indeed, there is stronger evidence for manipulation than for most orthodox medical treatments. The guidelines also advise that manipulation should be performed by a trained professional but that there is no clear evidence whether it is better performed by a chiropractor, an osteopath, a physiotherapist, or a doctor with special training.

Ernst and Assendelft's review of the risks of manipulation is particularly biased. Although the subject of this editorial is low back pain, they concentrate on the admittedly higher risks of cervical manipulation. Even then, orthodox medicine has a long way to go to reduce the rate of serious complications of most of our investigations and treatments to the order of 1:0.2-1 million. The adverse reactions to which the authors refer are temporary aggravations of symptoms or minor subjective reactions; in a personal series, that rate is comparable to figures for every other orthodox treatment for back pain. What matters is the balance of effectiveness versus risk, and that is strongly in favour of manipulation. The politics and costs of any NHS provision of a service are a completely separate and more relevant debate.

None of us have a good answer for low back pain—orthodox medicine, professors, and methodologists least of all. Chiropractic is not the magic answer for back pain, and it should and can stand up to fair criticism, but orthodox medicine could potentially also learn a lot from chiropractic.[5] The needs of patients with back pain should override our professional dignities, and the real need is for us all to work together. That cooperation is not likely to be helped by this kind of editorial.

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1 Clinical Standards Advisory Group. *Report on back pain.* London: HMSO, 1994.
2 Royal College of General Practitioners. *Clinical guidelines for the management of acute low back pain.* London: RCGP, 1996.
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5 Waddell G. *The back pain revolution.* Edinburgh: Churchill Livingstone, 1998.

### Editorial included topics unrelated to its title

Editor—Ernst and Assendelft's editorial is titled "Chiropractic for low back pain" but refers to cervical manipulations, potential overuse of radiographs by chiropractors, and a negative attitude of some chiropractors to immunisation.[1] Therefore, one must assume that a buckshot approach aimed fairly and squarely at chiropractic has been taken, as topics unrelated to the title of the editorial have clearly been included. The apparent attempt to define chiropractic intervention in the editorial's opening paragraph is incorrect, stating that, for example, chiropractic is used in the "hope of correcting vertebral disc displacements" and in the hope of correcting "spinal misalignment." Properly qualified chiropractors do not hope to correct "vertebral disc displacements" by manipulating the spine, as is implied. It would be stupid to contemplate manipulating the spine for disc displacement, by which the authors presumably mean extruded disc material. Spinal misalignment can be corrected by using an appropriate shoe raise when an inequality

in leg length and pelvic obliquity are the cause of the postural scoliosis (or spinal misalignment).[2]

Ernst and Assendelft have selectively cited the literature. For example, they cite two papers published in the *Journal of Manipulative and Physiological Therapeutics* (references 4 and 13) written by Assendelft et al (1996) and Assendelft and Bouter (1993). Why was the important paper by Terrett, in which he clearly cites misuse of the literature by medical authors in discussing spinal manipulative therapy injury,[3] selectively excluded when the editorial raises the issue of "cervical manipulations are burdened with severe adverse reactions such as vertebrobasilar accidents and paralyses due to fractures"? The only reference to this topic is by Assendelft et al (reference 5).

Ernst and Assendelft apparently saw it as appropriate that Ernst's paper on chiropractors' use of *x* ray films should be included (reference 8), as well as Ernst's paper apparently referring to the "negative attitude of some chiropractors towards immunisation" (reference 9).

Normally, scientific documents at least reflect the topic under discussion in the title, and in my opinion the editorial's title is misleading. Furthermore, from a scientific point of view it would be more appropriate to use references other than a preponderance of one's own to make a particular point and not to omit any pertinent reference, such as to Terrett's paper.

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1 Ernst E, Assendelft WJJ. Chiropractic for low back pain. *BMJ* 1998;317:160. (18 July.)
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3 Terrett AGJ. Misuse of the literature by medical authors in discussing spinal manipulative therapy injury. *J Manipulative Physiol Ther* 1995;18:203-10.
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### Authors' reply

Editor—The main focus of our editorial was on chiropractic and not spinal manipulation in general. For each favourable study cited in favour of chiropractic in these letters, at least one recent less favourable one can be found.

Breen addresses some apparent inconsistencies in our previous work. In one of our reviews[1] Meade et al's study did indeed rank as one of the methodologically best,[2] although the methods score was 48%. In this review Meade et al's trial was reported as positive because we followed the authors' conclusion. In a later review we made an independent judgment, on the basis of our interpretation of the clinical relevance of the results.[3] We considered the 2% difference on the Oswestry scale to be unconvincing. As Breen knows, our critique of Meade et al's study[4] was one of the starting points of the Medical Research Council's current trial that he describes, so the critique was probably less flawed than he implies.

Contrary to what Leerberg writes, we insist that there was no chiropractic study among the nine trials that Shekelle et al cited as favourable evidence for the effectiveness of spinal manipulation for low back pain.[5] Leerberg implies that we introduced inaccuracies by selectively citing reviews, but this is not the case. We cited Shekelle et al's review because it was the basis of several guidelines. We did not imply that chiropractic is less effective than manipulation in general. Leerberg states that we only selectively cited the literature on complications, but the cited reference by Terrett[6] is addressed in our review on complications.[7] We fail to understand what this reference would have contributed to our editorial.

Pedigro suggests that we should ask the many satisfied users of chiropractic. Indeed, in various studies patient satisfaction with chiropractic is relatively high. Although this is encouraging, we demand additional proof of effectiveness in terms of validly assessed increased functionality, decreased pain, or less absenteeism. Waddell states that "there is now considerable evidence that manipulation is an effective treatment." In the editorial we restricted ourselves to the effectiveness of chiropractic. Even for manipulation in general, however, our standpoint remains conservative. There are not yet enough methodologically sound randomised clinical trials that show strong, consistent, positive, and cost effective outcomes. The two most recent randomised controlled trials of chiropractic provide further support for our reserved attitude. Cherkin et al showed that for acute, uncomplicated back pain, both chiropractic and McKenzie physiotherapy lead to roughly the same results, which were not superior to those in controls who merely received an educational booklet, which previously had been shown to be ineffective.[8] The design of Skargren et al's trial[9] resembled that of Meade et al.[2] Half of the patients had acute back pain. The authors concluded that the effectiveness and total costs of physiotherapy or chiropractic, to reach the same results immediately after treatment and six months later, were similar.

We agree with Waddell that the risk-effectiveness balance is crucial, but insufficient data exist to allow us to evaluate this balance yet. Good prospective or case-control studies on complications are lacking.[7] Therefore, comparisons of complication rates with those for other, better evaluated treatments such as non-steroidal anti-inflammatory drugs are problematic.[10]

We also find positive messages in the letters. Breen acknowledges the need for further research, and both he and Waddell emphasise that a distinction should no longer be made between the various professions delivering spinal manipulation. Giles states that use of radiography and attitudes towards immunisation are irrelevant in relation to low back pain. This, however, is not the case; physicians want to be sure how a referred patient is approached. The challenge for national chiropractic associations is to develop clear standards of care addressing these issues and to change the behaviour of those practitioners who consistently overuse radiographs and interfere with immunisation programmes.

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1 Koes BW, Assendelft WJJ, van der Heijden GJMG, Bouter LM, Knipschild PG. Spinal manipulation and mobilisation for back and neck pain: a blinded review. *BMJ* 1991;303:1298-303.
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## Randomised block design is more powerful than minimisation

Editor—I agree with Treasure and MacRae that the greatest determinant of the power of a study is its design.[1] Minimisation improves power by comparing similar groups but there is a similar technique—randomised block design—which has even more power.[2]

In this design subjects are assigned to blocks on the basis of their characteristics—for example age, sex, or number of pack years smoked—and then randomly allocated to a treatment group within their block. In this way like is matched with like, and not only will the mean value of each confounding factor be similar in each group but the distribution will be identical in each treatment group. This means that the situation cannot arise in which two groups have the same average age but one comprises middle aged people and the other comprises half younger people and half older people.

The randomised block design also enables interactions of treatment with the blocked variables to be analysed; for example, is the treatment more effective in the elderly? The major disadvantage of this design is the same as in minimisation: assignment to a block becomes a major undertaking. However, this may be offset by the greatly increased power of the design, which results in smaller, cheaper trials.

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1 Treasure T, MacRae KD. Minimisation: the platinum standard for trials? *BMJ* 1998;317:362-3. (8 August.)
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## Identification of patients with atrial fibrillation in general practice

### Authors' reply

Editor—Roderick and Cox's work shows that it is feasible to identify patients with atrial fibrillation in clinical practice, which confirms the suggestions from our data. They say, however, that only a small proportion of those detected would be eligible for and would accept warfarin treatment. Their eligibility estimates are considerably lower than our own,[1] and we suspect that this difference partly reflects the effect of using different eligibility criteria, which we have noted previously.[2] Patients' understanding of the risks and benefits of treatment and their view of the possible outcomes are important determinants of the decision to treat and may also explain some of the differences between our estimates. Further work is required into methods for eliciting patients' preferences and incorporating them into the choice of treatment and into clear guidelines on the selection of patients for treatment.

We disagree with Fitzmaurice's assertion that the treatment effect of warfarin and the prevalence of atrial fibrillation remain unknown. Warfarin has been studied in several randomised controlled trials and has been shown to be superior to aspirin in patients with a high risk of stroke, who make up a high proportion of the population with atrial fibrillation.[1 3] The prevalence of atrial fibrillation in the United Kingdom has been reported in several surveys.[1 4 5] We would take issue with the more general point that "while we're there" research is dangerous. Assembling a representative sample of community patients is costly and time consuming. Once a sample has been identified it is an efficient use of resources to use data collected to address other pertinent issues.

We stated in our article that a trial of screening would be necessary before screening could be recommended. Our primary intention was to report on the characteristics of different tests that could be used to identify patients with atrial fibrillation and to facilitate further study. We believe, however, that there are currently more urgent priorities to address. The major needs are for guidelines to support appropriate selection of patients for anticoagulation (probably based around risk stratification schemes) and service developments to ensure that safe anticoagulation can be provided to minimise the risks of warfarin treatment. Nevertheless, the availability of a practical method to identify atrial fibrillation is a prerequisite for effective treatment. We hope that our article added to the evidence base on this issue.

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1 Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. *Lancet* 1998;352:1167-71.
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The authors' reply was inadvertently omitted from the cluster of letters on this topic that was published last week (p 191).

## Potential collaborators saw various problems with study of detoxification under anaesthesia

Editor—Brewer is correct when he states[1] that he invited us to collaborate on a trial of detoxification under anaesthesia[2] and that we did not take up this offer. We would not normally report publicly on such preliminary discussions or our reasons for not going ahead, but his letter clearly requires a reply.

Selection of appropriate study design and of collaborators of appropriate objectivity and equipoise is of great importance, since, as Kleber and Riordan have reminded us, "the history of narcotic withdrawal treatment is filled with 'cures' enthusiastically received and then quietly dropped when they turn out to be either ineffective, dangerous, or both."[3] Consequently, "any claims for a new method should be put forward with modesty and viewed with scepticism until amply documented by careful experimental procedures."

We chose not to collaborate with Brewer for various reasons. The professional reasons included our concern about the potential hazards of the procedure (several deaths have been reported, whether directly or indirectly related, including one under Brewer's own care[4]) and our dislike of Brewer's proposal that NHS funds should be diverted from the NHS into his private treatment business.

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1 Brewer C. Opiate detoxification under anaesthesia. *BMJ* 1998;316:1983-4. (27 June.)
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## Doctors don't see enough peaceful deaths

Editor—Goodall suggests that doctors are more afraid of death than is the rest of the population.[1] If she is right we must ask why this is so and question whether it might have a detrimental effect on the care given to very ill patients.

Recently I questioned eight junior hospital doctors about their experiences with patients dying in hospital. At the end of their first six months all had attended many cardiac arrests: one had been at 10, two at 15, two at 20, and the remaining three at more than 30. Their experiences of peaceful death contrasted with this. Three had been involved with a patient dying peacefully: one young woman said that she had sat and held a patient's hand as he died because he was alone and the nurses were too busy. Five, however, had never been at a peaceful death. It would be useful to find out if it is uncommon for a doctor to experience being with a patient dying quietly.

Doctors participate in many resuscitation attempts and witness many traumatic deaths. Death then probably appears a fearful event always to be avoided. If doctors (in contrast to nurses) never see a quiet and accepted death it may be difficult to recognise that a patient is dying and that sometimes he or she is ready to die. This may be detrimental to them giving good terminal care. This lack of experience of "good" deaths of patients in hospital or a hospice may have a serious impact on a person's feelings about his or her own mortality and impose a strain on young doctors.

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1 Goodall J. Doctors fighting, fleeing, or facing up to death. *BMJ* 1998;317:355-6. (1 August.)