

Drug combinations and all cause mortality in heart disease

No new insights were gained

EDITOR—Hippisley-Cox and Coupland conclude that the addition of angiotensin converting enzyme (ACE) inhibitors to combinations of drugs conferred no additional benefit in their study of patients in primary care with ischaemic heart disease.¹ However, such a conclusion should be reached with caution.

The drugs were given to the patients with the highest risk of death. A higher percentage of patients who died were treated with ACE inhibitors, and the greatest improvement in risk of death after adjustment for risk factors was seen in the patients treated with these drugs.

ACE inhibitors might thus have been given to the patients with the most severe disease in each comorbidity group—for example, to diabetic patients with kidney disease and to patients with the most severe heart failure. Therefore the study can give no indication of the crucial question whether the outcome would have been equally good for the group of 463 patients who probably had the most severe disease and received statins, aspirin, β blockers, and ACE inhibitors if they had not been given ACE inhibitors.

Replacement of yes or no for comorbidity factors with more discriminating variables, such as presence of microalbuminuria and a severity measure for heart disease, would probably have improved the study. However, this cannot replace the quality of a randomised, placebo controlled study comparing the effect of adding ACE inhibitors to the other study drugs. Therefore the study by Hippisley-Cox and Coupland adds no new knowledge to how patients with ischaemic heart disease in primary care should be treated.

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¹ Hippisley-Cox J, Coupland C. Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis. *BMJ* 2005;330:1059-63. (7 May.)

Use of statins is not supported by study

EDITOR—The key problem with the article by Hippisley-Cox and Coupland, who reported benefit from having been prescribed a statin, is outlined by a line in the discussion, according to which confounding by indication could have occurred if patients with a better prognosis were more likely to be prescribed different combinations of treatments.¹

High, rather than low, cholesterol concentrations are linked with greater statin use, and this selects the high cholesterol group, in which early death from heart failure is less² and general mortality in elderly patients is lower.^{3,4}

It is therefore unfortunate that Hippisley-Cox and Coupland say that treatment including statins improves survival rather than emphasising the simple point of selection bias—that is, of not being in the “low cholesterol” group of elderly people, where increased mortality may well be concentrated and cholesterol lowering treatment was not indicated.

This cohort study could lead to “could have” medicine, whereas in a high risk population of virtually identical age, the placebo controlled PROSPER study (surprisingly omitted as reference) found absolutely no mortality benefit but increased cancer in a statin group with fewer smokers.⁵

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¹ Hippisley-Cox J, Coupland C. Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis. *BMJ* 2005;330:1059-63. (7 May.)

² Horwich TB, Hamilton MA, MacLellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail* 2002;8:216-24.

³ Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. *Lancet*. 1997;350:1119-23.

⁴ Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu heart program: a cohort study. *Lancet* 2001;358:351-5.

⁵ Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623-30.

Dosages and types of ACE inhibitors need to be known

EDITOR—The study reported by Hippisley-Cox and Coupland leads to much generalisation.¹ Firstly, I am concerned that the data on angiotensin converting enzyme (ACE) inhibitors, contradict convention. Secondly, without actual data in front of me, I have to guess at the meaning of the ACE inhibitor data.

As the EUROPA, PROGRESS, ANBP, PEACE, TRACE, SAVE, and HOPE studies have shown, there is a great disparity in efficacy of ACE inhibitors. As Doulton et al say in their review of ACE inhibitor and angiotensin receptor blocker trials, the ACE inhibitor trials were described as mostly using submaximal doses or a once daily dose of shorter acting ACE inhibitors.² It has long been known that the more efficacious trials of ACE inhibitors used a large dose, as the perindopril investigators found out in PROGRESS and EUROPA. The trandolapril investigators also saw this disparity in PEACE and TRACE. What were the ACE inhibitor doses in the trial reported by Hippisley-Cox and Coupland?

Another consideration is the order in which these drugs were given. If a β blocker is given first the drop in blood pressure will, for the most part, urge clinicians to give a lower dose of ACE inhibitor subsequently. These are submaximal doses.²

I cannot reach the conclusions that Hippisley-Cox and Coupland came to, without a better understanding of the raw data.

Then, there is the concept of equality in ACE inhibitors. Although a larger dose is good, does it still have the same effect as another ACE inhibitor might have? The MITRA-plus trial serves as an example here. This indicates the possibility of another disparity.

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¹ Hippisley-Cox J, Coupland C. Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis. *BMJ* 2005;330:1059-63. (7 May.)

² Doulton TW, He FJ, MacGregor GA. Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. *Hypertension* 2005;45:880-6.



References and links for studies are on bmj.com

Authors' reply

EDITOR—There can be no substitute for a properly conducted randomised controlled trial in determining effectiveness of different treatments. All observational studies, however carefully designed and analysed, are subject to unmeasured confounding, as we point out in our paper. We think our study adds to the work on the Polypill by Wald and Law in providing more direct evidence on combinations of individual treatments as used in clinical practice in the United Kingdom.

Firstly, we conducted an analysis restricted to patients without diabetes, congestive cardiac failure, or myocardial infarction, to deal with confounding by indication. As we reported in the paper, the results of the restricted analysis showed little change in the odds ratios for the various combinations of treatment except for angiotensin converting enzyme (ACE) inhibitors alone. For example, the adjusted odds ratio for the combination of statins, aspirin, and β blockers was 0.20 (95% confidence interval 0.11 to 0.37) and that for statins, aspirin, β blockers, and ACE inhibitors was 0.36 (95% confidence interval 0.15 to 0.88). This shows that confounding by indication was not a substantive source of bias in our analysis.

Secondly, Snyder requested more data on the pattern of usage of different ACE inhibitors, which are shown in the table. This pattern reflects the rank order for prescriptions dispensed nationally according to UK prescribing analysis and cost data. This shows that a variety of ACE inhibitors were in use at the time of the study and that no particular preparation dominated the findings. We do not think that we have sufficient power to undertake further analyses comparing individual ACE inhibitors or an analysis by dose, particularly in combination with the other treatments.

Thirdly, Vos raises the issue that the PROSPER study did not show a reduction in all cause mortality with pravastatin. However, mortality due to coronary heart disease fell by 24%.¹ Also, the weight of the evidence from randomised controlled trials supports the hypothesis that statins improve survival for patients with ischaemic heart disease.²⁻⁵

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- 1 Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623-30.
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Citizen jury should consider aspirin prophylaxis

EDITOR—I smiled to read that the jury was still out on aspirin to prevent cardiovascular disease in elderly people in This week in the *BMJ* because, of course, there has never been any sort of jury on this topic.¹⁻² This debate about aspirin has consumed the medical profession for over 30 years, yet almost no public participation or consultation has occurred.

Although aspirin has benefits, it is considered inappropriate for people with known contraindications. Its effects in symptom free subjects cannot be predicted. Standard advice is that subjects should consult a doctor before starting aspirin prophylaxis. However, perhaps patients, not doctors, should evaluate for themselves the possible outcomes and make decisions on the basis of their own evaluation of the risks and benefits.

Aspirin is not an alternative to health promotion or behavioural change in relation to exercise and diet. Nor is it a substitute for the appropriate treatment of high blood pressure. The possibility of a simple low dose pill taken daily, with the potential to achieve reductions in vascular events and even cancer and dementia requires serious consideration, as well as greater public discussion and participation in the debate.

Perhaps the public should be asked, for example, "Should every person over 50 in the United Kingdom be taking aspirin on a daily basis?" Such a debate would be a good model for illustrating the perennial questions in medicine about benefits outweighing harms, the extent to which decision making about preventive health measures should be shared between patients and professionals, and how best to involve the public

in discussions about taking individual responsibility for health, a key objective in current healthcare policy. A citizens' jury on aspirin would be a good first step forward.

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- 1 This week in the *BMJ*. Aspirin to prevent cardiovascular disease in elderly people: the jury's still out. *BMJ* 2005;330. (4 June.)
- 2 Nelson MR, Liew D, Bertram M, Vos T. Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged 70. *BMJ* 2005;330:1306. (4 June.)

Aspirin for everyone over 50?

Avoid the harm

EDITOR—The recommendation that everyone over 50 should take aspirin ignores the issue of dose with its ratio of benefit to risk, given that a person still has at least a third of life span remaining and that older hypertensive patients are susceptible to haemorrhagic stroke.¹ The debate about what is a low dose has gone on long enough, with no definite answer beyond 75 mg to over four times its multiple at 325 mg for secondary prevention of cardiovascular and cerebrovascular thrombotic disease. Aspirin across the board for primary prevention may be considered in patients with a 10% risk of coronary heart disease, and the risk-benefit balance between the number of myocardial infarctions that can be prevented and the risk of haemorrhagic stroke and gastrointestinal bleeds must be taken into account.

Bandolier has looked at randomised controlled trials in patients at low risk of cardiovascular disease and failed to find sufficient evidence of benefit.² A meta-analysis of subjects at moderate risk indicates that the risk of thrombotic stroke is overemphasised and overpowers the risk of major bleeds even from low dose aspirin.³

Cost is often a limiting factor in Trinidad and Tobago, where enteric coated or slow release preparations, which may reduce the incidence of gastrointestinal blood loss, are not available in the public sector and are unaffordable for many patients. Patients must take responsibility for their health, but if they are also expected to choose their treatment, why do they need a doctor?

The evidence of benefit for aspirin as primary prevention in influencing cardiovascular outcomes is still awaited. Meanwhile, avoid the possible harm.

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- 1 Elwood P, Morgan M, Brown G, Pickering J. Aspirin for everyone older than 50?: FOR. *BMJ* 2005;330:1440-1. (18 June.)
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Pattern of angiotensin converting enzyme inhibitor use in cases and controls

	No (%) of cases (n=2226)	No (%) of controls (n=9064)
Patients not taking ACE inhibitors	1140 (50.3)	5463 (60.3)
Total patients taking ACE	1126 (49.7)	3601 (39.7)
Lisinopril	349 (15.4)	1169 (12.9)
Ramipril	240 (10.6)	732 (8.1)
Enalapril maleate	211 (9.3)	740 (8.2)
Perindopril tert-butylamine	126 (5.6)	364 (4.0)
Captopril	131 (5.8)	351 (3.9)
Other*	69 (3.0)	245 (2.7)

*Cilazapril, fosinopril, unipril, trandolopril, moexipril, imidapril.

The buck stops in the consulting room

EDITOR—Surprisingly, Elwood et al let the medical profession off the hook about the risks of aspirin prophylaxis for myocardial infarction.¹ To put the onus of decision taking on the patient, instead of the doctor being an informed mentor in the fight against vascular disease, is alarming.

How is the concept that “each person, not a doctor, should evaluate the risks and benefits” valuable in making a decision to a patient who is unaware of drugs and pharmacotherapeutics? The authors also advise that patients “are likely to accept a small increased risk of bleed or other side effect in exchange for a reduced risk of a heart attack or stroke.” This is indirectly offered medical advice from doctors. Passing the buck is impossible when the buck stops here, in the consulting room.

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Don't forget aspirin resistance

EDITOR—None of the authors in the debate for and against the prescribing of aspirin for those over 50 mentions the growing notion of aspirin resistance.^{1,2} This term is used to describe not only an absence of the expected pharmacological effects of aspirin on platelets but also poorer than expected clinical outcomes. Thus, in biochemical aspirin resistance the in vitro activation of platelets is persistent, and in clinical aspirin resistance patients taking aspirin have recurrent vascular events.

Several studies have now shown that a substantial minority of patients may have either total or partial aspirin resistance.³ Although these studies may have methodological differences, they suggest that between 5% and 55% of treated patients may have some degree of aspirin resistance. Recent data suggest that a substantial proportion of patients at a potentially greater risk of cardiovascular events than a normal population have aspirin resistance.⁴

Whether aspirin related side effects are less common in aspirin resistant patients is unknown. If they are not, then universal aspirin administration may be associated with an increase in side effects with no concurrent decrease in cardiovascular events.

Until these issues have been further investigated, it seems unwise to recommend aspirin for everyone over 50.

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Are we treating a nutritional deficiency?

EDITOR—If as many as 80% of men and 50% of women over 50 will benefit from taking aspirin then perhaps a non-disease approach should be considered.¹ Could the effects of aspirin be mimicking a nutrient missing in the modern/civilised diet? As reported in *New Scientist*, organically grown vegetable soups contain almost six times more salicylic acid than do non-organic vegetable soups.² Morgan has suggested that salicylates are essential for good health and could be designated vitamin “S.”³

Many commonly used medicinal herbs contain substances that the body biotransforms to salicylic acid. For example, salicin is found in *Salix* spp, *Populus* spp, *Viola* spp, and *Viburnum* spp; fraxin is found in *Fraxinus* spp; and both spiraein and salicylaldehyde are found in *Filipendula* spp.^{4,5} These substances are biotransformed after passage through the stomach and so are not associated with the risks of gastrointestinal bleeding, as is aspirin.^{6,7} Salix extracts have several anti-inflammatory targets, including effects on both forms of cyclo-oxygenase.⁸

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1 Elwood P, Morgan M, Brown G, Pickering J. Aspirin for everyone older than 50: FOR. *BMJ* 2005;330:1440-1. (18 June.)

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5 Mills S, Bone K. *Principles and practice of phytotherapy*. London: Churchill Livingstone, 2004:61.

References w1 and w2 are on [bmj.com](#)

Authors' reply

EDITOR—The case for the wider use of aspirin in vascular prophylaxis arises from the belief that subjects should be empowered to make their own decision about protecting their own health. This will be achieved only if information on the risks and benefits of preventive measures, including low dose aspirin, is widely available.

Granted, the numerical risk-harm balance of aspirin in trials based on subjects at low vascular risk is equivocal. If people are to be adequately informed, they should be told this, but they should also be told that the degree to which subjects in these trials were representative of the community is unknown. People should also be reminded that an evaluation of risks and benefits is also highly dependent on the seriousness and the consequences of the possible outcomes. In the end, people have the right to make this evaluation and decide about prophylaxis themselves, and enabling them do so is hardly passing the buck.

We caution against the use of enteric coated tablets and advise soluble preparations.¹ However, we find the paucity of evidence on the absorption and side effects of low dose aspirin in different formulations and taken in various ways worrying. Were aspirin still under patent, the available and new formulations would undoubtedly be fully investigated, but funding for such studies is unlikely to be available.

We reserve judgment on aspirin resistance. The relevance to vascular events of the usual platelet tests is doubtful.² Furthermore, most patients who would have been judged to be aspirin resistant show the expected responses when aspirin is taken under supervision.³

The suggestion that non-pharmacological approaches be considered is of wide interest. Most plants contain salicylates, and the reduced cancer risk in vegetarians is just one strand in the evidence from disparate sources suggestive of a reduction in cancer risk by aspirin.^{4,5}

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Clinical leadership in hospital care

Leadership and teamwork skills are as important as clinical management skills

EDITOR—Olsen and Neale conclude that improving leadership and teamwork skills among today's doctors is both important and necessary.¹ However, opportunities in everyday hospital medicine to acquire, practise, and receive feedback on these skills remain scarce.

Unlike other industries—such as aviation, which allow experienced team members to observe teams in their work environment, thereby enabling structured feedback on leadership and team behaviours—medicine has not yet placed adequate importance and resources into training clinical teams in similarly important non-technical skills.

The focus of undergraduate teaching and postgraduate advanced life support

courses remains the acquisition of technical skills and delivery of health care in the context of one doctor, one patient.

Competent practitioners must learn to interact in and eventually lead teams of healthcare workers, yet little or no formal teaching is aimed at developing individual doctors' leadership skills or to helping them to understand the impact of their behaviour and actions on the team.

Simulation training is one way of developing, practising, and gaining insight into non-technical skills. Careful consideration of course aims and attention to maximising equipment, environmental, and psychological fidelity can build the right environment for teams of doctors, nurses, and other healthcare workers to acquire leadership and teamwork skills.²

Opportunities for feedback and acquisition of leadership and teamwork skills, be it in a real or simulated clinical environment, should become an established part of postgraduate training. The current focus on acquiring technical skills alone is too narrow and should be seen as a failure of medical training.

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- 1 Olsen S, Neale G. Clinical leadership in the provision of hospital care. *BMJ* 2005;330:1219-220. (28 May.)
- 2 Gosling N, Moore M, Williams C, Festa M. Can simulation recreate a realistic and appropriately stressful environment to observe team behaviours in the setting of paediatric critical illness? *Arch Dis Child* 2005;90(SII):A82.

The right kind of clinical leadership is needed

EDITOR—Olsen and Neale are right to point to the importance of clinical leadership in reducing adverse events in hospital care.¹ What is required, however, is not the leadership beloved of politicians, where bullish confidence and decisiveness, often in the face of considerable opposition, are the order of the day. Rather, an atmosphere of trust in the clinical team is needed so that the most junior members of staff, or even the patient's relative, have the confidence to raise concerns about the quality of patients' care.

This approach is being pioneered by the Health Foundation in partnership with the Institute of Healthcare Improvement in its safer patients' initiative. Launched in 2004, the £4m initiative involves four acute trusts from across the United Kingdom that will become models of excellence in patients' safety.

The conventional leadership, trust board and clinical directors, has a crucial part to play in encouraging safe practice through demonstrating its importance, collecting data, and showing a willingness to listen to issues that concern clinical teams and acting on them. But the key is education and training of staff to adopt proved safer practice and to adapt it to the situation in which they find themselves.

Thus leadership needs to be shared throughout the system so that those nearest

to the problem can identify its causes, offer solutions, and take action, all the time feeling confident that they are being listened to and backed by senior staff. Although it is early days for the safer patients' initiative, the Health Foundation is committed to providing evidence that investing in leadership leads to improvements in the quality of patients' care. Evaluation findings from its portfolio of work will be made available as work progresses.

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- 1 Olsen S, Neale G. Clinical leadership in the provision of hospital care. *BMJ* 2005;330:1219-220. (28 May.)

Mother to child transmission of HIV in China

Chinese HIV sentinel surveillance data were used incorrectly

EDITOR—Chen and Han misleadingly interpret data in their editorial on mother to child transmission of HIV in China.¹ Using data from sentinel surveillance, they conclude that two provinces, Henan and Xinjiang, have a "worrying" HIV prevalence among pregnant women of over 1%.

Firstly, sentinel surveillance sites are concentrated in areas thought to have a higher prevalence of HIV, since surveillance functions largely as a case detection process, and it is not intended to be representative of the whole population.

Secondly, much larger sample sizes are necessary to be representative of these large provinces as the numbers of women participating in surveillance are few and the prevalence of HIV is low. For example, Henan has a population of 96 million with over 1 million births yearly and the highest number of HIV infections in commercial blood donors. The authors quote an HIV prevalence of 1.4% for the whole province on the basis of a sample of only 500 pregnant women, who came mainly from the areas where the prevalence of blood donor related infection is known to be high. Likewise in Xinjiang (population 20 million) HIV is strongly associated with injecting drug use, so sentinel surveillance of pregnant women is focused where there are many drug users. Extrapolating these figures to whole provinces makes no sense because they will clearly overestimate the prevalence.

The authors do not comment on the comparatively low prevalence in Yunnan province (0.37%). Yunnan has the longest standing epidemic, the highest cumulative reported number of cases of HIV, and the best sentinel surveillance coverage. It is the only province with reasonable data on secular trends in pregnant women. These show fluctuations since reporting started in 1992 with increases from 0.3% in 1996 ($n = 5972$) to 0.37% in 2003.²

As elsewhere, surveillance sites are concentrated in high risk areas, probably

overestimating the prevalence for the whole province. But this comparatively modest increase should perhaps be regarded as a positive finding that may bode well for the future trajectory of the epidemic in China.

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- 1 Chen KT, Qian H. Mother to child transmission of HIV in China. *BMJ* 2005;330:1282-3. (4 June.)
- 2 Yunnan Centre for Disease Control. HIV/AIDS Statistics. Kunming: Yunnan Centre for Disease Control, 2004.

Authors' reply

EDITOR—We agree with Hesketh et al that caution should be applied in extrapolating HIV prevalence data among pregnant women at sentinel sites to the general female population. In countries with a concentrated epidemic, such as China, where HIV is well established in certain subpopulations, sentinel surveillance is needed to target the groups at highest risk and initiated among pregnant women.¹

The overriding value of surveillance is its use as a tool to identify the potential emergence of infectious diseases and to guide actions to prevent them from becoming threats to public health.² Without universal HIV testing of pregnant women in China, the information obtained from the existing sentinel surveillance sites is the best estimate we have of the HIV prevalence in pregnant women. The finding that two provinces in China have HIV prevalences over 1% in a sample of pregnant women is an alert that HIV may have transmitted from high risk groups to the general population. More representative HIV prevalence rates in pregnant women are needed in China. One strategy of voluntary counselling and testing in pregnant women in China should yield more information.^{3 4}

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- 1 World Health Organization. Joint United Nations Programme on HIV/AIDS. *Guidelines for second generation HIV surveillance*. Geneva: WHO/UNAIDS, 2000.
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