Letters

Angiotensin receptor blockers and myocardial infarction

Analysis of evidence is incomplete and inaccurate

Editor—Verma and Strauss say that, compared with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers do not reduce (and may increase) the risk of myocardial infarction.[1] Their claim represents an incomplete, inaccurate, and misleading "analysis" of the evidence.

They did not cite the two largest studies that randomised patients to an ACE inhibitor or angiotensin receptor blockers and had the statistical power to evaluate cardiovascular outcomes.[2 3] These had twice as many myocardial infarctions as their trials combined (table). As none of their trials randomised these two treatments, their conclusions depend on indirect comparisons, small numbers of events and are unreliable. OPTIMAAL (379 patients with MI in the captopril group and 384 losartan) and VALIANT (798 total myocardial infarctions in captopril group, 796 valsartan) strongly refute the authors' hypothesis.

Other data were selectively and incorrectly cited—for example, mentioning the only CHARM trial with an excess of myocardial infarctions in the candesartan group (the other two trials had fewer) and inaccurate citation of the risk increase (table).[4] That the losartan group in RENAAL had fewer myocardial infarctions was not mentioned. It is no surprise that angiotensin receptor blockers failed to reduce mortality in trials underpowered to test for this.[5] The interpretation of trials using an active control is confounded when these can reduce myocardial infarction (for example, a β blocker) or lower blood pressure more (for example, amlodipine).[w1 w2]

A correct analysis would have considered all relevant data, appropriately weighted, and composite non-fatal and fatal outcomes, to take account of competing risks.

We endorse the need to obtain (and disclose) evidence from randomised trials to support the use of new drugs. Seeing such a misleading opinion in the *BMJ* does a disservice to the proper evaluation of drug efficacy and safety, as well causing unnecessary anxiety for patients.

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Competing interests: All authors have been or are involved in clinical trials with angiotensin receptor blockers in cardiovascular disease and have received honorariums for speaking, consultancy fees, and research grants from pharmaceutical companies that market angiotensin receptor blockers.

Treatments and cardiovascular outcomes in trials

Trial	Patients' condition	Treatments	No of patients	Follow-up in years	No of patients with myocardial infarction*
IDNT	Diabetic nephropathy	Placebo	569	2.6	51
		Irbesartan	579		48
		Amlodipine	567		29
RENAAL	Diabetic nephropathy	Placebo	762	3.4	68
		Losartan	751		50
SCOPE	Elderly hypertension	Placebo	2460	3.7	63
		Candesartan	2477		70
LIFE	Hypertension Left ventricular hypertrophy	Atenolol	4588	4.8	188
		Losartan	4605		198
VALUE	Hypertension risk factors	Amlodipine	7596	4.2	313
		Valsartan	7649		369
CHARM	Heart failure	Placebo	3796	3.1	190
		Candesartan	3803		176
OPTIMAAL	Myocardial infarction	Captopril	2733	2.7	379
		Losartan	2744		384
VALIANT	Myocardial infarction	Captopril	4909	2.1	559
		Valsartan	4909		587
		Captopril and valsartan	4885		554

*Fatal or non-fatal.
CHARM: candesartan cilexitil in heart failure: assessment of reduction mortality and morbidity. IDNT: irbesartan in diabetic nephropathy trial. LIFE: losartan intervention for endpoint reduction in hypertension. OPTIMAAL: optimal trial in myocardial infarction with the angiotensin II antagonist losartan. RENAAL: reduction in endpoints in patients with non–insulin-dependent diabetes mellitus with the angiotensin II antagonist losartan. SCOPE: study of cognition and prognosis in the elderly. VALIANT: valsartan in acute myocardial infarction trial. VALUE: valsartan antihypertensive long-term use evaluation.

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Details of the eight coauthors and additional references w1 and w2 are on bmj.com

Results reflect different cardiovascular states in patients with types 1 and 2 diabetes

Editor—Verma and Strauss's editorial supports the contention that angiotensin receptor blockers are associated with increased risk of myocardial infarction.[1] Included in the documentation of this risk are briefing documents from the US Food and Drug Administration quoting data from the irbesartan diabetic nephropathy trial.[2] However, the authors did not cite our published analysis of cardiovascular events during this trial.[3] Omitted was any mention that the difference between irbesartan and placebo or amlodipine did not reach significance with respect to myocardial infarctions ($P>0.2$ and $P=0.068$, respectively). Neither were death rates different.[2]

A meta-analysis cited in the editorial used faulty logic.[4] Its conclusion emphasised that mortality in studies of diabetic nephropathy using angiotensin converting enzyme (ACE) inhibitors was lower than in studies using angiotensin receptor blockers, with the erroneous implication that ACE inhibitors are safer. Most patients in studies using these drugs had type 1 diabetes mellitus, whereas the studies using angiotensin receptor blockers included patients with type 2 diabetes. Our large captopril trial used ACE inhibitors in type 1 diabetic nephropathy.[5] All placebo controlled trials that used angiotensin receptor blockers studied type 2 diabetes.

The average age in the captopril trial was 35 and in the irbesartan trial 59. Three per cent of patients in the placebo group and 3.9% in the captopril group ($P>0.3$) experienced a myocardial infarction during the course of that study. In the irbesartan trial, these rates were 8% in the placebo and

7% in the irbesartan groups.[2] All cause mortality in the placebo group in the irbesartan trial was 16.3% compared with 6.9% in the placebo group in the captopril trial.[2 5]

The discrepant mortality and rates of non-fatal myocardial infarction for the placebo groups in these two studies are accurate reflections of the marked difference in the cardiovascular status of patients with type 1 and older patients with type 2 diabetes. The implication that difference in these risks could have been explained by the class of renoprotective agent employed is ludicrous.

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Direct comparative studies are needed

EDITOR—The editorial by Verma and Strauss does not accord with the *BMJ*'s usual impartial evidence based approach.[1] Evidence that angiotensin receptor blockers increase myocardial infarction is scant, and I remain puzzled about what exactly patients should be told—that the *BMJ* published an incorrect analysis?

Regarding angiotensin receptor blockers and myocardial infarction in hypertension, the data from the valsartan antihypertensive long term use evaluation (VALUE) trial, quoted by Verma and Strauss, can be added to a prior meta-analysis by the Blood Pressure Trialists.[2] The incidence of coronary heart disease and myocardial infarction is 804/16061 (5%) in the treated groups and 763/15948 (4.78%) in the controls (odds ratio 1.046), a non-significant increase of myocardial infarction of 4.6% *v* controls, whereas lisinopril increased combined cardiovascular disease by 10%.[3]

Regarding candesartan and heart failure, in the predefined group of patients with low left ventricular ejection fractions (<40%), candesartan reduced all cause mortality by 12% (P=0.018), and the composite end point including myocardial infarction by 16% (P<0.001).[4]

Regarding diabetic nephropathy, they misquote the meta-analysis of Strippoli et al, which specifically concludes that because there are very few head to head comparisons of angiotensin receptor blockers with angiotensin converting enzyme (ACE) inhibitors, their relative survival effects remain unknown.[5] Clearly, both these types of agents are of substantial clinical value. New data show potentially additive renoprotection, implying potentially different fundamental mechanisms. ACE inhibitors first changed cardiovascular treatments, and now angiotensin receptor blockers need to be fully tested in direct comparative studies.

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Cautions voiced are biologically credible

EDITOR—We agree with Verma and Strauss that it is naive to consider that angiotensin receptor blockers are like angiotensin converting enzyme (ACE) inhibitors, but without the cough.[1] Although the evidence is conflicting, the hypothesis that angiotensin receptor blockers may predispose to myocardial infarction when used in preference to ACE inhibitors warrants further attention.

Long term clinical benefits of treatment with ACE inhibitors, including reduction in fatal and non-fatal myocardial infarction, are well established in chronic heart failure, hypertension, and after myocardial infarction.[2] These benefits persist, although serum concentrations of angiotensin II return to pre-treatment values after long term treatment with ACE inhibitors.[3]

This implies that the mechanism(s) of benefit from ACE inhibitors extend beyond simple antagonism of angiotensin II. The effects of ACE inhibitors are related to the upstream blockade of the renin-angiotensin axis, which not only attenuates the conversion of angiotensin I to angiotensin II but also inhibits the degradation of kinins to inactive metabolites. ACE inhibitors, and not angiotensin receptor blockers (which block the renin-angiotensin axis at its most distal, type I receptor site), therefore result in raised concentrations of bioactive kinins such as bradykinin.[4]

This fundamental difference is important since bradykinin has several beneficial actions—antiarrhythmic effects and reduction of infarct size mediated through ischaemic preconditioning and vascular protection mediated by nitric oxide or prostacyclin.[4] In addition, the hypothesis has some rationale that angiotensin II type II receptors, as well as the type I receptors, may have potentially deleterious effects in cardiovascular disease.[5]

The cautions voiced by Verma and Strauss are biologically credible, and we therefore advise that until these issues are resolved, angiotensin receptor blockers should be used with caution in subjects who are perceived to be at a high coronary risk.

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Authors' reply

EDITOR—We agree with McMurray et al that angiotensin receptor blockers have not been associated with increased myocardial infarction in all trials, although viewing myocardial infarction in concert with cardiovascular death may be more appropriate. For example, in OPTIMAAL cardiovascular mortality was higher with losartan (relative risk 1.17, 95% confidence interval 1.01-1.34) and myocardial infarction did not change. In RENAAL losartan actually decreased myocardial infarction by 26% and delayed the need for dialysis by 40 days, but once dialysis was required the mortality in the losartan group was 29% higher.[1]

The VALIANT rate of myocardial infarction had not been published previously, and we thank the trialists for providing this information. VALIANT lasted only 24.7 months, and 39% of the patients received angiotensin converting enzyme (ACE) inhibitors before randomisation (average day 5). Early administration of these drugs after myocardial infarction reduces 30 day mortality by 7% with 85% of that benefit in the first week,[2] thereby potentially masking differences between ACE inhibitors and angiotensin receptor blockers. VALIANT proved the "non-inferiority" of valsartan to captopril, but this does not imply equivalence of treatment, rather simply that valsartan is "not substantially worse."[3]

CHARM-ADDED and OVERALL were not discussed since the rate of myocardial infarction for candesartan without ACE inhibitors in the background could not be

ascertained. In LIFE the β blocker atenolol does not seem to be anti-ischaemic. A meta-analysis in almost 25 000 hypertensive patients confirmed that atenolol significantly reduces blood pressure, but has no reduction in myocardial infarction, death, or stroke.[4] According to some experts,[5] the 19% difference in blood pressure rate (P = 0.02) seen in VALUE cannot be explained by blood pressure difference in favor of amlodipine, nor by "serial median matching."

Results of placebo controlled trials in coronary artery disease with both amlodipine (CAMELOT) and nifedipine (ACTION) confirm that calcium channel blockers improve symptoms of angina, reduce need for angiography or revascularisation, and reduce blood pressure, but they do not decrease myocardial infarction or death, implying that blood pressure differences or vascular benefits of amlodipine were not responsible for the heightened myocardial infarction rate with valsartan.

With respect to Lewis's and Opie's comments, it is important to point out that captopril in reference 5 of Lewis's letter reduced mortality by 40%, whereas irbesartan compared with placebo in the irbesartan diabetic nephropathy trial (IDNT) did not reduce mortality or myocardial infarction despite a reduction of 4/3 mm Hg in blood pressure.[w1] A meta-analysis in diabetic kidney disease confirms that ACE inhibitors and angiotensin receptor blockers are similar and powerful nephroprotective agents.[w2] However, ACE inhibitors significantly reduced all cause mortality (relative risk 0.79, 95% confidence interval 0.63 to 0.99), whereas angiotensin receptor blockers did not (0.99, 0.85 to 1.17). Furthermore, the aetiology of the diabetes did not affect the benefit. In patients with diabetes, the benefit of ACE inhibitors has been well established by MICRO-HOPE and PERSUADE.[w1]

The body of evidence supporting both myocardial and mortality benefit of ACE inhibitors greatly exceeds that of angiotensin receptor blockers, which is probably why most worldwide guidelines recommend it first line across the disease spectrum.[w3]

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Additional references w1-w3 and for eight named studies are on bmj.com

Reducing mortality in myocardial infarction

Primary angioplasty has strong evidence base

EDITOR—A short ambulance ride from the tertiary cardiac centre from where Townend and Doshi expound the virtues of prehospital thrombolysis plus early revascularisation lies a district hospital that has operated a policy of primary angioplasty for more than two years.[1]

In this hospital, which is staffed by four cardiologists (see author list), more than 200 primary angioplasty procedures have been performed, with a 30 day mortality of 6.5%, reduced hospital lengths of stay, and a long term cost effectiveness that is comparable to thrombolysis. Although sometimes inconvenient, cases in truly unsocial hours (midnight to 8 00 am) represent only 20% of the total primary angioplasty burden.

Few now dispute the evidence for primary angioplasty.[2] As yet there are no robust data showing the superiority of prehospital thrombolysis over primary angioplasty. CAPTIM was not completed,[3] and a quarter of the study population required rescue angioplasty for failed reperfusion. Townend and Doshi do not clearly state their position on the management of failed thrombolysis. GRACIA 1 merely shows that thrombolysed patients are probably better off with revascularisation before discharge rather than later, irrespective of whether ongoing ischaemia is shown (the open artery hypothesis).[4] Several ongoing and planned trials will elucidate whether facilitated intervention (thrombolysis plus angioplasty within three to 12 hours) is superior to primary angioplasty.

Until the case for primary angioplasty is undermined in appropriate randomised trials perhaps we should be striving to introduce the optimal and proved strategy, concentrating on an evidence based rather than convenience based approach.

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Goal should be interhospital transfer for primary angioplasty

EDITOR—In their editorial on reducing mortality from myocardial infarction Townend and Doshi did not point out two advantages of primary percutaneous coronary intervention: long term benefit and better preservation of working ability, with consequent reduction of direct and indirect costs of coronary heart disease.[1]

One size fibrinolytic treatment with streptokinase is associated with worse long term clinical outcomes than primary percutaneous coronary intervention, especially in myocardial infarction with anterior ST segment elevation.[2 3]

The largest contributors to the expenditure of coronary heart disease are indirect cost of lost productivity resulting from morbidity and mortality (50.2% of the total cost of coronary heart disease in the USA in 2005) and hospital charges (28.1%).[4] As shown by Le May et al, the primary percutaneous coronary intervention is cost saving compared with thrombolysis.[5] However, indirect costs would also be expected to be lower, because this strategy reduced days of hospitalisation. The waiting list for percutaneous coronary intervention will shorten and the return to work rates will increase.

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Experience in Cuba shows optimising thrombolysis may reduce death rates in poor countries

EDITOR—The epidemic of cardiovascular disease has peaked in Cuba and accounts for 40% of deaths.[1] The age adjusted mortality in 2003 was 41% lower than the comparable rate recorded in 1970. The reduction in mortality from coronary heart disease, which accounts for nearly 74% of all cardiovascular deaths, drove the overall decline in cardiovascular mortality.[1] Data from Cuba are highly accurate since registration has been consistently high over this 30 year period and deaths attributed to ill defined causes have remained very low (0.7%). Nearly all deaths are certified by a doctor.

In Cienfuegos province, Cuba's showcase for prevention and control of cardiovascular disease, the number of admissions for acute myocardial infarction doubled in 1990-2003. Over the same period, case fatality rates declined by 40-50%, which implies that less severe cases are being admitted, although the quality of care is also improving. This latter possibility is supported by the fact that over this period, thrombolysis—the standard treatment in Cuba—became widely available, and this was recently reinforced with the creation of prehospital treatment units in each municipality. In addition, Cienfuegos Hospital achieved a total thrombolysis rate over 60% and a "door to needle" time of around 30 minutes for more than 90% of all patients with acute myocardial infarction and ST elevation.[2 3]

We recognise the importance of a "three Ps" approach[4] and consider that in poor countries the optimisation of thrombolysis (including the promotion of the "golden hour") can still reduce mortality from acute myocardial infarction before angioplasty is introduced. Given Cubans' high level of education, the country's universal access to health care, and its large public health infrastructure, an exceptional opportunity exists here to answer some of the questions associated with thrombolytic treatment, particularly in the context of a public, accessible, and free health system for all.

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Illness trajectories are also valuable in critical care

Editor—I was uplifted by the simple wisdom of Murray et al and suggest that the concept of illness trajectories has value in critical as well as palliative care.[1] Intensivists are often referred patients with similar trajectories to those presented,[1] where a catastrophe so dominates the presentation that an immediate attempted rescue is undertaken before the opportunity is taken to appraise both the less evident underlying trajectory and the acute event. An example is the frail elderly patient with dementia and multiple comorbidities who presents with a "potentially curable" fungating mandibular tumour.

Even previously well patients develop faster "trajectories of dying" after admission to intensive care units. I have noted a trend to attempt escalated rescue of increasingly daunting complications in dying patients. An example is the patient with severe pancreatitis who develops infected necrosum, then intra-abdominal abscesses, and finally drain associated erosion of retroperitoneal vessels.

Since predicting survival of a critically ill individual is imprecise, all patients should receive good end of life care from the moment of admission to intensive care, even though most will survive their critical illness. Murray et al's figure 2 conveys this concept well.[1]

Critical care seems stuck in the old paradigm—a moment before which there is only a "curative" objective and after which only a "comfort" objective.[2] This paradigm is clearly unsatisfactory when a patient takes an unfavourable illness trajectory, and it can deprive the patient and family of time to prepare for death while "curative" treatments are escalated and emotional and spiritual needs are neglected.

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Emergency endoscopy service could be provided

Editor—Douglass et al describe a failure and diversity in the provision of services for emergency endoscopy throughout the United Kingdom.[1] We recently reported our outcomes of upper gastrointestinal bleeds, using the model of a dedicated bleed unit with a 24 hour emergency endoscopy service.[2] Our risk adjusted mortality was lower than that described in the National Audit (crude mortality: our unit 8.1% *v* National Audit 14%, $P < 0.001$).

This demonstrable improvement (having adjusted for case mix) may be for two reasons. Firstly, the rate of endoscopy within 24 hours was higher (94.2%) than in the National Audit (70.9%). Secondly, the creation of a dedicated bleed unit that allows joint medical and surgical evaluation, implementation of predefined protocols, and monitoring by specialist nursing staff. This service is analogous to coronary care units and ensures the optimal management of patients with upper gastrointestinal bleeding.[2]

How can the provision of such a service be met throughout the UK? With the implementation of European working time directives, trainees cannot be expected to have the experience to perform endoscopy independently at night. Recent data show that endoscopists' experience may be an independent prognostic indicator.[3] For these reasons our department has adopted the approach of a consultant delivered service with the appropriate remuneration (24 hours on call, followed by a day in lieu). This service incorporates 10 consultants and provides regional support to the surrounding district general hospitals.

We consider that a dedicated bleed unit with a consultant delivered service is the optimal solution to the issues raised by Douglass et al. However, this is only possible with the mutual cooperation of or robust negotiations with trust management. This service may not only provide a better quality of care for the patients (with improved outcomes) but can also be potentially cost effective with the earlier discharge of low risk patients.[4]

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Nature and doctors can be dangerous

Editor—Farrell always writes with pith and verve, but in his most recent article he misses the point.[1] We are all familiar with the "natural" paradigm—our patients offer us daily examples. But when patients use the word "natural," they are using a code or euphemism.

They are saying that biomedical intervention is risky, potentially harmful, damaging, and suspect and that doctors as pedlars of this system may be untrustworthy. We can contest this view as much as we like, but it is hard to disentangle ourselves from this perception without sounding dismissive or defensive. And no matter how hard we strive, we still inadvertently cause harm. I know exactly what my elderly patients mean when they volunteer that they "don't want to be mucked about." They are using different phrases to express the same concerns as those who ask for natural remedies.

The natural movement is a reaction to patriarchal medical practice, a form of resistance. Of course nature is dangerous and unpredictable, or as Wordsworth said "red in tooth and claw." But the real irony is that the view that all things natural must be good is underpinned by the same multinational interests that govern biomedicine. Divide and rule.

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1 Farrell L. Au naturelle. *BMJ* 2005;330:1033. (30 April.)