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Angiotensin receptor blockers and myocardial infarction

These drugs may increase myocardial infarction—and patients may need to be told

The interpretation of large scale clinical trials is being increasingly scrutinised by leading journals,[1] with great emphasis being placed on the importance of sharing all potential side effects, no matter how trivial, with patients. The *Lancet* recently published the results of the valsartan antihypertensive long term use evaluation (VALUE) trial, a study of the effects of reducing blood pressure in patients at high risk.[2] The angiotensin receptor blocker valsartan produced a statistically significant 19% relative increase in the prespecified secondary end point of myocardial infarction (fatal and non-fatal) compared with amlodipine. A doctor who is a patient of one of the authors (SV) commented that if the incidence of myocardial infarction increased with valsartan it would be an essential component of informed consent to share this information when prescribing valsartan for high risk patients with high blood pressure. These peculiar results led us to examine carefully the evidence surrounding angiotensin receptor blocker and myocardial infarction.

Could the unexpected increase in the incidence of myocardial infarction in the VALUE trial represent a statistical aberration? Although the modest, yet significant differential in blood pressure in favour of amlodipine (1.8 mm Hg systolic and 1.5 mm Hg diastolic *v* amlodipine) may explain the 13% increase in the incidence of stroke in patients taking valsartan (P = 0.08), it is unlikely, according to some experts, to account for the 19% increase in the incidence of myocardial infarction.[3]

Unfortunately careful evaluation of the current evidence shows that angiotensin receptor blockers, unlike angiotensin converting enzyme inhibitors, are either neutral or increase the rates of myocardial infarction despite their beneficial effects on reducing blood pressure.

For example, the CHARM-alternative trial showed a significant 36% increase in myocardial infarction with candesartan (versus placebo) despite a reduction in blood pressure (4.4 mm Hg systolic and 3.9 mm Hg diastolic *v* placebo treatment).[4] Likewise, in the CHARM-preserved study, candesartan reduced admissions for chronic heart failure by 13% but did not prevent death despite a mortality of 11.3% and a reduction in blood pressure of 7 mm Hg systolic and 3 mm Hg diastolic compared with placebo.[5] In the study on cognition and prognosis in the elderly (SCOPE), candesartan was associated with a non-significant 10% increase in fatal plus non-fatal myocardial infarction despite lower blood pressure (3.2 mm Hg systolic and 1.6 mm Hg diastolic for candesartan *v* placebo).[6] Furthermore, the angiotensin receptor blocker losartan in the LIFE study did not reduce rates of myocardial infarction despite a 1.7 mm Hg lower pulse pressure compared with atenolol.[7] In the RENAAL trial, a study performed in diabetic patients with nephropathy, the angiotensin receptor blocker losartan offered nephroprotection, but no reduction in cardiovascular mortality, although about 30% of patients died of a cardiovascular event.[8] In a similar population the angiotensin receptor blocker irbesartan showed nephroprotection[9] but seemed to have no impact on the 24% incidence of cardiovascular events (a secondary composite end point). Although irbesartan lowered blood pressure (4 mm Hg systolic and 3 mm Hg diastolic *v* placebo), no reduction occurred in myocardial infarction, stroke, or cardiovascular death. Compared with amlodipine, irbesartan was associated with a 36% increase in non-fatal myocardial infarction (P = 0.06), a 48% non-significant increase in stroke, and a 29% non-significant increase in death despite similar blood pressure reduction (see advisory briefing of the Food and Drug Administration, NDA 20-757 (S-021), www.fda.gov).

These peculiar effects of angiotensin receptor blockers on myocardial infarction stand in contrast to those of angiotensin converting enzyme inhibitors, which consistently produce a 20% or greater reduction in myocardial infarction in patients with diabetes, hypertension, renal insufficiency, and atherosclerosis.

How could two pharmacological agents, considered by many to be interchangeable and equivalent, have such divergent effects on coronary vascular outcomes despite similar effects on blood pressure? Medicine contains several examples of similar pharmacological conundrums. For example, metformin and phenformin, agents of the same class that have similar effects on insulin sensitivity and glycaemic control, have different side effects, and phenformin is associated with a higher rate of lactic acidosis. Troglitazone, rosiglitazone, and pioglitazone are all thiazolidinedione insulin sensitisers, yet troglitazone was removed from the market because of increased rates of hepatocellular necrosis. Different

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statins have different side effects. Furthermore, pharmacological agents that held great promise for cardiovascular protection, such as hormone replacement therapy, have proved to be ineffective. If such profound differences exist between drugs in the same class, is it prudent to consider angiotensin receptor blockers and angiotensin converting enzyme inhibitors, drugs from two different classes, similar? Levy has recently provided some insight into how the angiotensin type II receptors may have harmful as well as beneficial effects.[10]

Has the time has come for clinicians, scientists, pharmacologists, and ethicists to review the unexpected effects of angiotensin receptor blockers on myocardial infarction and determine whether this should be part of the discussions between doctors and patients when starting treatment? In the interim, clinicians need to remember that treatment with valsartan at the initial dose used in the VALUE trial (80 mg) was associated with a significant increase in the incidence of myocardial infarction compared with amlodipine at the initial dose of 5 mg, although the incidence of cardiovascular death did not differ. Antihypertensive efficacy should not be confused with vascular protection, and until the results of large comparative trials such as ONTARGET/TRANSCEND[11] are available, it may be naive to consider that angiotensin receptor blockers are like angiotensin converting enzyme inhibitors but without the cough. Indeed, a recent comparison of these two classes of agents in diabetic nephropathy, has revealed a lack of benefit of angiotensin receptor blockers on mortality, despite renal protection.[12]

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The Mexico Summit on Health Research 2004

Fine words, few actions

See also News p 1258

The time: four days, 25 working sessions, six round tables, six joint plenaries and "networking" lunches. The people: hundreds of international delegates, 29 ministers of health, and 29 ministerial representatives. The result: three firm action points, seven vague ones. The reason: political expediency.

The Mexico Summit on Health Research was a historic gathering of health ministers—let's not quibble that only 29 bothered to turn up—and just as many ministerial representatives. The ministers spoke with passion, and surprising understanding, of challenges facing health systems research. The advocates—public health specialists, researchers, and technocrats from the World Health Organization—put their case to ministers with clarity, and surprising persuasiveness.

But what will the millions of poor people in our world make of the Mexico Agenda for Health Research, a document agreed by health representatives from 59 states? What will they make of the call for action that makes only three points that can be immediately translated into actions?

The first of these is a commitment to producing national research agendas. The world's poor could say: "Thank you, but you have been promising us these for 20 years. How do we know that this time it is different, and how do we know that research agendas will make a difference any time soon?"

What then about the commitment to supervise a network that will coordinate the various clinical trial registries and make them talk to each other and the world in a transparent manner? The world's poor could say: "Thank you, but much of the research that affects our lives is not clinical trials. Trial registration is a good start but how do we know that this good practice will spread to the majority of health systems research any time soon?"

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