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The Divergent Cardiovascular Effects of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Myocardial Infarction and Death

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ABSTRACT

The renin angiotensin aldosterone system (RAAS) plays a central role in the pathophysiology of hypertension and vascular disease. Angiotensin converting enzyme inhibitors (ACEis) suppress angiotensin II (ANG II) concentrations, whereas angiotensin receptor blockers (ARBs) block the binding of ANG II to AT_1 receptors. ACEis and ARBs are both effective anti-hypertensive agents and have similar risk reductions in stroke — a blood pressure dependent phenomenon. ACEis also reduce the risk of myocardial infarction (MI) and mortality in high risk hypertensive patients, as well as in diabetics, the elderly, those with vascular disease, and in congestive heart failure. ARBs, in contrast, do not reduce the risk of MI or death in clinical trials where the comparator has been another active therapy or even a placebo. Systematic reviews of ARBs that include meta-analyses or meta-regression analyses confirm that ARBs lack the cardiovascular protective effects of ACEis, which in part are "independent" of blood pressure lowering. Practice guidelines, especially those in high risk hypertensive patients, should reflect the evidence that ACEis and ARBs have divergent cardiovascular effects — ACEis reduce mortality, whereas ARBs do not. ACEis should be the preferred RAAS inhibitor in high risk patients.

Angiotensin converting enzyme inhibitors (ACEis) and angiotensin II type 1 (AT_1) receptor blockers (ARBs) are anti- hypertensive (HTN) agents that modulate the renin angiotensin aldosterone system (RAAS) by targeting angiotensin II (ANG II), each with a unique mode of action. ACEis suppress the production of ANG II, whereas ARBs block the ANG II stimulation of the AT_1 receptor; therefore each is a unique therapeutic class. ACEis and ARBs do have similar blood pressure (BP) lowering effects, with a positive impact on stroke,[1] diabetic kidney disease,[2] symptoms of congestive heart failure (HF),[3] and at least in *post hoc* analyses of large clinical trials, reduce the incidence of diabetes mellitus(DM) and atrial fibrillation.[4] This shared efficacy has led to the conclusions in many practice guidelines that ACEis and ARBs are equivalent, interchangeable, and alternative

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Abbreviations and Acronyms

ACEi = angiotensin converting enzyme inhibitor

ARB = angiotensin receptor blocker

BP = blood pressure

CHD = coronary heart disease

CV = cardiovascular

CVA = cerebral vascular accident

DM = diabetes mellitus

HF = heart failure

HTN = hypertension or hypertensive

LV = left ventricular

MI = myocardial infarction

NYHA = New York Heart Association

QoL = quality of life

RAAS = renin angiotensin aldosterone system

SBP = systolic blood pressure

therapies, and to perhaps be viewed as a single pharmacologic class — "RAAS inhibitors".[5,6] This conclusion however, is not shared by all.

In the most recent iteration of the European Society of Hypertension (ESH) guidelines,[7] section 5.2.1.4 states that *"angiotensin receptor blockers may be inferior to ACE inhibitors in preventing myocardial infarction (424) or all-cause mortality (393)."* This statement might be viewed by many as controversial, if not heretical. However, if the BP reductions seen with ARBs do not translate into a reduction of "hard" cardiovascular (CV) endpoints similar to ACEis, then ACEis should be the preferred RAAS inhibitor in high risk patients. There is compelling and robust evidence to support this conclusion, such as clinical trial data in approximately 300,000 patients. The results are consistent whether from individual trials with a placebo or active comparator, or in meta-analyses,[8–10] or meta-regression analyses that adjust for BP within the trials[1,11]; ACEis reduce the risk of myocardial infarction (MI)and death above and "independent" of BP lowering, whereas ARBs do not.

This review will focus on the "hard" CV endpoints of ACEi and ARB trials – MI and death – in the context of the known impact of BP lowering per se on these endpoints. As well, the trial data will be evaluated from the perspective of its design and the statistical analysis used – prospective vs. retrospective trial, double blind vs. open label, active or placebo comparators, statistical "superiority" or "non-inferiority" – as any conclusion of therapeutic efficacy is predicated on the strengths and limitation of the statistical analysis used.

BP and CV endpoints

The CV endpoints of greatest clinical importance in the treatment of hypertension are mortality, MI, and stroke (CVA) — the "hard endpoints". The relationship of BP and mortality was assessed in a collaborative meta-analysis of prospective observational studies in 1,000,000 subjects with no known CV disease, thus evaluating the potential impact of BP reduction independent of any additional cardio-protective effects drugs might provide.[12] For every 10 mmHg reduction in systolic BP (SBP), it was predicted that the risk of coronary heart disease (CHD- MI plus CV death) would decrease by 25% and CVA by 36%. Although the risk reduction in CHD is less than CVA, death from CHD is three times more common than from CVA — confirming that CHD is the primary target for the greatest benefit to the population. This prediction was confirmed in a meta-analysis of 147 randomized anti-HTN trials by Law and Wald[13] — for every 10 mmHg reduction in SBP, CHD decreased 22% and stroke 41%. Although this meta-analysis includes a broad range of anti-HTN agents, each class may not provide equivalent reductions in the "hard endpoints"[1,11,14] which is an important consideration in the choice of therapeutic agents. It is also clinically relevant to consider the therapeutic benefits of anti-HTN on "soft" endpoints – microalbuminuria, insulin resistance, uric acid, tolerability, etc. – but primarily when the impact on "hard endpoints" is similar.

The ARB MI paradox – the evidence is there from 2004

A 2004 editorial in the *British Medical Journal*[15] (co-authored by one of us: MHS) was the first reference in the literature to suggest that ARBs may not provide similar CV protection as ACEis. Early ARB trials appeared not to reduce the risk of MI or death despite demonstrating good tolerability and effective BP lowering.[15] It was noted in the VALUE[16] trial that there was a statistically significant 19% excess of MI with the ARB valsartan as compared to the calcium channel blocker amlodipine in a large population of HTN patients. Other ARB trials also observed small increases in the risk of MI[4] — which achieved statistical significance in the CHARM-Alternative study.[17] There was biologic plausibility to explain this phenomenon – as discussed below – which was termed the "ARB MI Paradox".

The *BMJ* editorial[15] was controversial but resulted in tremendous discussion and debate which were addressed six months later at the 2005 European Society of Hypertension Meeting in Milan. The Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC)[1] presented a parallel meta-regression analysis of ACEi and ARB trials where BP differentials within the trials were regressed against the risk of MI and death-CHD. Both ACEis and ARBs were shown to have identical BP "dependent" risk reduction of CHD. However, for any given BP reduction, ACEis reduce the risk of CHD an additional 9% (p = 0.002) above and "independent" of the effects of BP lowering with the 9% relative risk reduction apparent even in the absence of any BP reductions (Fig 1)[1] — a phenomenon confirmed by others.[11,18] In contrast, ARBs have no BP "independent" effects on CHD, rather there is a small non-significant increase in the risk of harm of 7% (95% CI; 24%–7%, p = ns) (Fig 1). For any given BP reduction, ACEis reduce the risk of MI and death an additional 15% (p = 0.0001) above that of an ARB, which was "independent" of BP lowering (Fig 1). In contrast, the risk reduction in stroke and HF for ACEis and ARBs were each identical and solely dependent on BP lowering. The BPLTTC meta-regression analysis[1] validated the hypothesis put forth in the *BMJ* editorial[15] – that ARBs lack the cardioprotective effects of ACEis on CHD – thus confirming the "ARB MI Paradox".