FEATURED EDITORIAL

More about the "*ARB MI paradox*"

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"Logic dictates that angiotensin converting enzyme inhibitors should remain the preferred drug across the entire spectrum of cardiometabolic disease"

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Introduced into clinical practice in 1995, the angiotensin receptor blockers (ARBs) selectively antagonise the angiotensin II AT_1 receptor, producing effects that include reduction of aldosterone release and hence, also, of salt and water retention. ARBs are effective for the treatment of hypertension, symptomatic congestive heart failure, and for the prevention of stroke. Furthermore, ARBs are effective in preventing progression of diabetic nephropathy and may also prevent atrial fibrillation. In all of these clinical situations, ARBs seem to share the same benefits as previously seen from treatment with angiotensin converting enzyme inhibitors (ACEi). ACEi and ARBs both reduce angiotensin AT_1 receptor-mediated events, albeit through distinct pharmacological mechanisms.

MECHANISMS OF ACTION

The mechanism of action of ACEi differs from that of ARBs in a number of ways, which include differential effects on bradykinin breakdown, nitric oxide, prostacyclin, COX-2 activity, and each has a diametrically opposite effect on the angiotensin II AT_2 receptors. ACEi reduce activation of AT_2 by reducing angiotensin II levels, whereas ARBs augment baseline angiotensin II levels and thereby augment AT_2 activation. These differences, have been widely used to suggest that the newer ARBs might have important advantages over ACEi—and, in particular, might be more tolerable. Advocates of ARBs have been keen to suggest that "*ARBs are ACEi without the cough*"—namely, that ARBs have similar (or better) clinical efficacy, while at the same time being better tolerated. Based, at least in part, on this type of thinking, use of ARBs has increased to the extent that a similar amount of money is currently spent on ARBs in the UK each year (£45.9 million per quarter and 1.8 million items) as is spent on ACEi.[1 2] This observation correlates with the fact that generic ACEi are cheaper (eg, ramipril capsules 5 mg costs £2.38/28 days; fig 1) than non-generic ARBs (eg, losartan 50 mg costs £18.09/28 days). The pattern of increased use of ARBs is incongruous with all the major guidelines, which recommend ACEi as first-line treatment, and reserve ARBs for patients shown to be intolerant of ACE inhibition.[3 4] It is fiscally responsible, as well as clinically important, to determine the relative merits of these drugs.

In 2004 the VALUE trial reported their findings based on a 4.1-year comparison of the ARB, valsartan (up to 160 mg/day), and the calcium channel blocker, amlodipine (up to 10 mg/day), in 15 245 patients with high-risk hypertension. One key observation was that myocardial infarction (MI) was significantly more common in patients given the ARB (hazard ratio = 1.19 (95% CI 1.02 to 1.38), p = 0.02), an effect that some have attributed to the inferior antihypertensive response of the ARB treatment.[5 6] Importantly, a debate sparked which has focused on the mechanism, rather than on the reality, of a failure of ARBs to prevent the occurrence of MI.[7 8] The fact that valsartan was a less effective antihypertensive drug than amlodipine is an observation that does little to recommend ARBs as first-line treatment, regardless of the underlying mechanism for the excess MIs observed.

EFFECTIVE DOSE

Some have suggested that the dose of valsartan used in VALUE may have been inadequate,[9 10] and that 160 mg twice a day should be the recommended target dose, a dose that was used in the VALIANT trial. VALIANT compared the effects of high-dose valsartan with captopril 50 mg three times a day in patients after MI heart failure.[11] The tolerance profile of high-dose valsartan relative to captopril puts this into a different perspective (table 1). The occurrence of cough was less common with the ARBs, as also were rash and taste disturbances, both of which are symptoms directly attributable to the sulphydryl molecular subgroup that distinguishes captopril from the more commonly used carboxyl ACEi (eg, ramipril, perindopril). However, high-dose valsartan was associated with a clear excess of hypotension and renal dysfunction, particularly when used in combination with captopril. Furthermore, the overall treatment intolerance rates were no different in the ACEi and ARB arms. This information challenges the perception that ARBs are intrinsically better tolerated than ACEi—especially when both are given at "*effective doses*".

ARB META-ANALYSES

In August 2006, the journal *Circulation* published a detailed analysis of the "*ARB-MI paradox*" with a set of papers debating whether ARBs may actively increase the risk of MI across a wide range of disease states.[12 13] Both sets of authors agreed[14 15] on the following key points:

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; CV, cardiovascular; MI, myocardial infarction

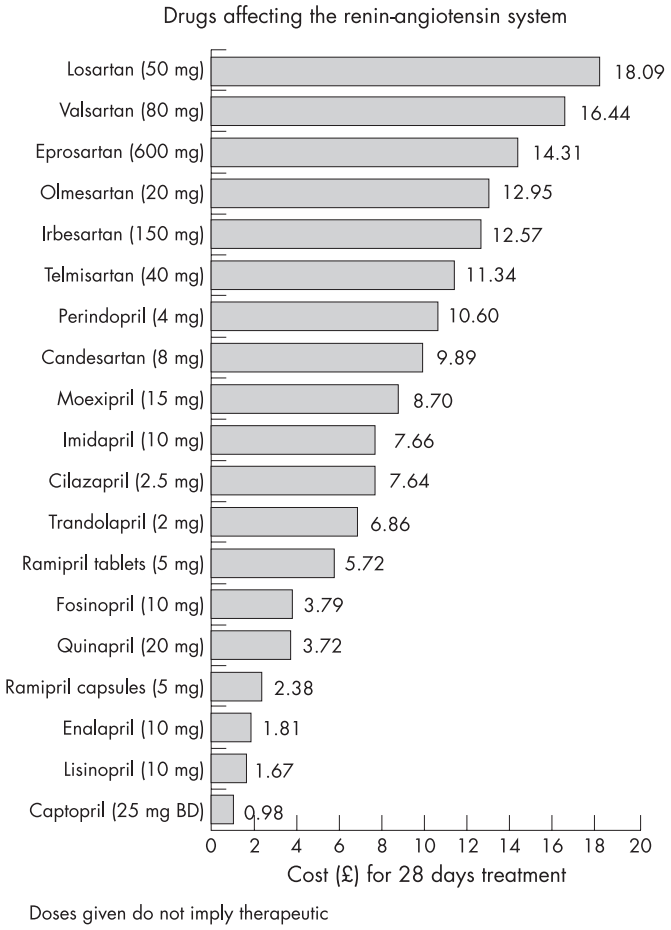

Figure 1 Cost comparison charts January 2007. Reprinted with permission from the Regional Drug and Therapeutics Centre (Newcastle).[1]

- ACEi can prevent both MI and cardiovascular (CV) death.
- ARBs do not prevent MI or CV death.
- ACEi should be considered to be better than ARBs in this respect.
- ACEi should be used as first-line treatment across the entire cardiometabolic vascular spectrum of disease.

The two papers differed slightly in their results for reported ARB meta-analyses for the relevant randomised controlled trial data (table 2). Strauss and Hall reported an 8% (95% CI 1% to 16%, p = 0.03) excess of MI for ARB as compared with non-ARB control arms; while Tsuyuki and McDonald reported only a 3% (95% CI −7% to 13%, p = 0.59) excess of MI. Although some small differences in the MI rates reported for some trials were apparent, the main distinction between these two meta-analyses related to (*a*) the studies included; (*b*) the statistical test used. Tsuyuki and McDonald claimed to have included all trials irrespective of study size, study duration, concomitant use of ACEi, or indeed the absence of published data. For example, the unpublished MI data from the MOSES Study[16] was included based on a ''*personal communication*''. Unfortunately, the ''communication'' did not make it clear whether multiple events for individual patients were included—as reported for stroke in the main published analysis for MOSES.[16] If so, then it is conceivable that a single patient randomised to nitrendipine might have had 20 recurrent events as compared with 17 patients given eprosartan who might each have had a fatal MI event. The clinical significance of either of these two possible scenarios is quite different. Although inclusivity is an important attribute of a meta-analysis, this must be weighed against the use of appropriate, prespecified, systematic inclusion criteria. In this regard, it should be noted that other potentially relevant unpublished data were not included—for example, from the RESOLVD pilot study.[17] Perhaps a ''personal communication,'' would have been relevant, especially considering that the RESOLVD pilot was stopped prematurely owing to excess CV events with candesartan.[17]

In addition to the ARB meta-analyses of Strauss and Hall and Tsuyuki and McDonald, two other ARB meta-analyses (Verdecchia and Volpe) also confirm that ARBs do not reduce MI or CV death, and both showed a trend for an increase in MI,[10] as did Tsuyuki. The lack of reduction in MI and CV death seen in all four ARB meta-analyses contrasts sharply with an ACEi meta-analysis by Strauss and Hall of over 150 000 patients. ACEi reduced MI by 14% and CV death by 12% in patients with similar CV risks as the ARB meta-analysis (risk of MI about 6%, and risk of CV death about 9%). Of note, two recent meta-regression analyses comparing ACEi with ARBs (BPLTTC)[18] or calcium channel blockers (CCB),[19] respectively, confirm that ACEi reduce MI and CV death by an additional 9–12% above that predicted by blood pressure lowering alone, confirming a benefit of ACEi that is independent of blood pressure.[18]

In conclusion, there is no dispute about the major clinical efficacy associated with the use of ACEi across a wide spectrum of CV disease states (table 3).[12] In contrast, the efficacy of ARBs

Table 1 Adverse events leading to treatment dose reduction or discontinuation in the VALIANT Trial[11]

Adverse event	Valsartan (320 mg/day)	Valsartan and captopril	Captopril (150 mg/day)
ACEi vs ARB excess			
Cough	85 (1.7)*	225 (4.6)	245 (5.0)
Rash	32 (0.7)*	53 (1.1)	61 (1.3)
Taste disturbance	13 (0.3)*	38 (0.8)	31 (0.6)
ARB vs ACEi excess			
Hypotension	739 (15.1)*	884 (18.2)	582 (11.9)
Renal causes	239 (4.9)*	232 (4.8)	148 (3.0)
ARB = ACEi			
Any reason	2103 (43.1)	2342 (48.2)	2098 (43.0)

Results are shown as No (%)
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
*Indicates p<0.05 relative to captopril
Note: January 2007 UK cost per 28 days of captopril 50 mg = £0.98; valstartan 80 mg = £16.44 (see ''Cost comparison charts''[1] and fig 1).

Table 2 Comparison of two meta-analyses of ARB trials and incidence of MI[12 13]

Trials	Number of MIs	Strauss and Hall	Tsuyuki and McDonald	Comment
Group 1 : No concomitant use of ACEi and ARBs				
Large placebo controlled trials	454	Included	Included	Both analyses include these major trials, though have slightly
Large active controlled trials	1093	Included	Included	different MI rates for ELITE-1 and DETAIL that reflects poor
ARB versus ACEi trials	1990	Included	Included	reporting of MI in published papers
10 Very small trials	35	Not included*	Included	Trials lasted only a few weeks being designed to assess immediate effects on blood pressure
MOSES study	37	Not included*	Included	Not published
RESOLVD pilot	?	Not included	Not included	Inconsistency in T and M analysis
Group 2: Partial concomitant use of ACEi and ARBs				
CHARM—preserved Val-HeFT		Not Included*	Included	Confounds comparison of ACEi vs ARB effects
Group 3: Complete concomitant use of ACEi and ARBs				
CHARM—Added		Not Included	Included	Confounds comparison of ACEi vs ARB effects Inconsistency in T and M analysis
VALIANT—Combined arm		Not Included	Not Included	
Summary of meta-analyses				
Total number of MI events (patients)		3537 (54 050 patients)	4039 (68 711 patients)	
Sensitivity analyses		Yes (see above)	No	Sensitivity analyses provide robustness to observations
Assessed CV death		Yes	No	Consistent trend as for MI
Parallel ACEi analysis		Yes	No	Adds robustness to comparison
Test for heterogeneity		χ^2 = 11.7 (p = 0.32)	χ^2 = 31.1 (p = 0.12)	Both show absence of heterogeneity
Statistical test used		Fixed effect	Random effect	Fixed effects model is most appropriate
Hazard ratio (95% CI)		1.08 (1.01 to 1.16)	1.03 (0.93 to 1.13)	Both exclude benefit from ARBs
p Value		0.03	0.59	

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; MI, myocardial infarction.
*Although not appropriate for systematic main analysis, trials added for sensitivity analysis, hazard ratio = 1.07 (95% CI 1.00 to 1.14; p = 0.05).

Table 3 Meta-analysis results for ACEi and ARBs assessing a range of ''hard'' cardiovascular end points[12]

End points	Number at risk	Number of events	Control event rate (%)	Odds ratio (95% CI)	p Value overall effect
ACEi vs placebo/non-ARB comparator/ARBs					
Global death	150 943	18 643	13.0	0.91 (0.86 to 0.95)	<0.001***
CV death	143 663	11 847	8.4	0.88 (0.82 to 0.95)	0.001***
Non-CV death	142 653	6 184	4.7	0.98 (0.93 to 1.04)	0.56
Stroke	135 803	5 485	4.2	0.94 (0.83 to 1.06)	0.31
MI	144 790	8 377	5.8	0.86 (0.82 to 0.90)	<0.001***
ARBs vs placebo/non-ACEi comparator/ACEi					
Global death	55 050	7 601	14.0	1.01 (0.96 to 1.06)	0.80
CV death	54 050	5 028	9.2	1.01 (0.95 to 1.07)	0.71
Non-CV death	54 050	2 562	4.7	1.00 (0.93 to 1.09)	0.89
Stroke	53 318	2 285	4.4	0.92 (0.79 to 1.08)	0.32
MI	54 050	3 537	6.3	1.08 (1.01 to 1.16)	0.03*

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; MI, myocardial infarction.
*p<0.05; ***p<0.001.

seem to be limited mainly to surrogate clinical end points that include blood pressure, renal function, and signs and symptoms of heart failure. Efficacy with regard to major clinical end points (other than stroke) seems to be much more limited with ARBs—and in the case of MI, absent all together. Furthermore, these distinct profiles are based on intention to treat analyses and so take into account any differences in treatment compliance/tolerance. Importantly, direct comparison of higher and presumably more ''*effective doses*'' of ARBs with ACEi shows tolerability to be equivalent.

Given these observations, and also the important concerns about the ''*ARB-MI paradox*'' it seems pertinent to ask why healthcare providers should spend substantially more money (per prescription) on ARBs than ACEi. Logic dictates that ACEi should remain the preferred drug across the entire spectrum of cardiometabolic disease.

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IMAGES IN CARDIOLOGY

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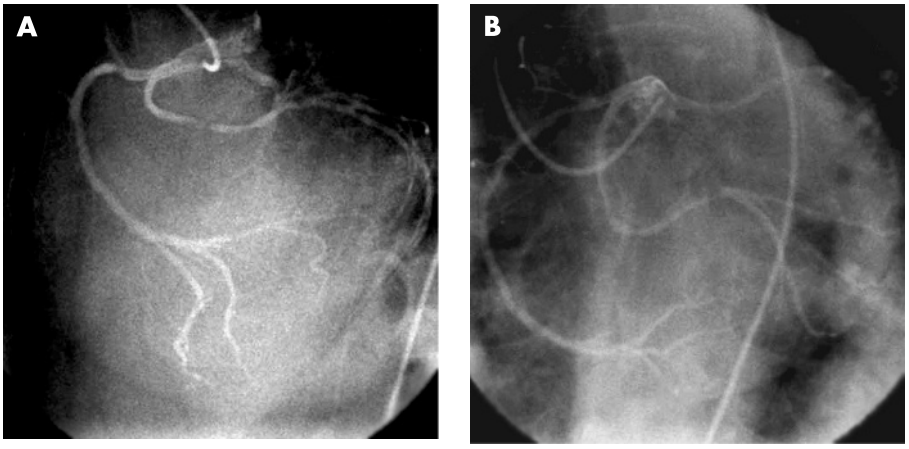
Common origin of all three major coronary vessels from the aorta through a single ostium

A 42-year-old man with a history of heavy smoking (3–4 packs/day) for more than 20 years and a strong family history of premature coronary artery disease underwent coronary angiography after initial management for non-ST-elevation myocardial infarction. A coronary angiogram disclosed an anomalous coronary anatomy with common origin of the left anterior descending (LAD), circumflex and right coronary arteries (RCA) with critical three vessel disease. The RCA showed an 80% lesion in the proximal third, the circumflex had a 90% lesion in the middle third, and the LAD was totally occluded just after the origin of a large diagonal one branch (panel A). He underwent bypass grafting and did remarkably well. An anteroposterior view clearly demonstrated the common origin of the LAD, RCA and circumflex arteries (panel B). As far as we know, this is the first reported case of all three coronaries originating from a single ostium from the aorta.



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