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Angiotensin II receptor antagonists for the treatment of heart failure: what is their place after ELITE-II and Val-HeFT?

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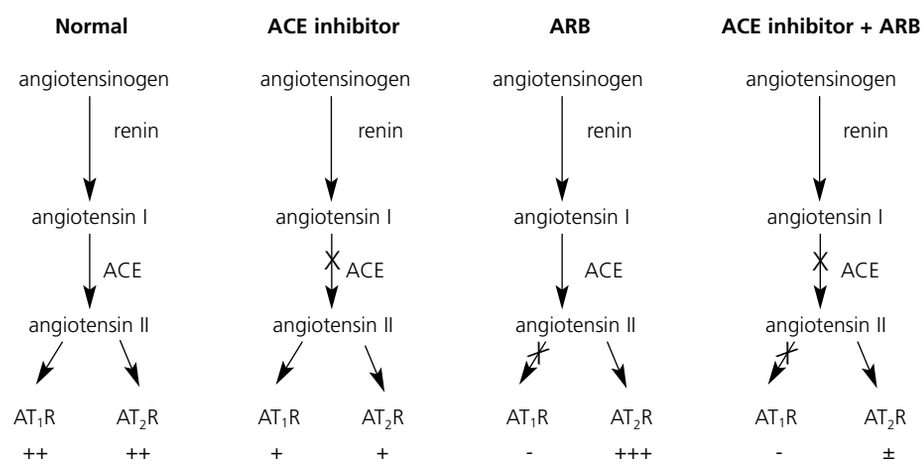
Introduction

Certain drugs that block the renin-angiotensin-aldosterone system (RAAS), namely angiotensin converting enzyme inhibitors (ACE-I) and spironolactone, have been shown to improve symptoms, reduce hospital admission rates and increase survival in patients with chronic heart failure (CHF).[1-5] Consequently, angiotensin II (Ang II) type 1 receptor antagonists or Ang II type 1 receptor (AT_1-receptor) blockers (ARBs) may also have a role in the treatment of CHF. Two therapeutic strategies have been considered for ARBs, the first as an alternative to ACE-I[6–9] and the second in combination with ACE-I.[10–12] Interestingly, the rationale behind these strategies is quite different. In the first, the kinase II property of ACE is considered disadvantageous, in that bradykinin is directly or indirectly blamed for the undesirable effects of ACE-I such as cough and angio-oedema.[6,7] The second strategy sees bradykinin as a desirable substance, with vasodilator, anti-thrombotic and growth inhibiting properties.[10–12] Both strategies, however, regard ACE-I as sub-optimal antagonists of the action of Ang II, reflecting the belief that non-ACE pathways also contribute to the generation of Ang II (and this can only be blocked by an ARB).[13–15] An even more theoretical difference between ACE-I and ARBs concerns the postulated role of the Ang II type 2 receptor (AT_2-receptor). This receptor is considered by some to exert the opposite effects to the AT_1-receptor.[16] ACE inhibition leads to reduced stimulation of both types of Ang II receptor, whereas selective AT_1-receptor blockade, in theory, leads to hyperstimulation of the unblocked AT_2-receptor. The alternative strategy of combination ACE-I and ARB therapy in CHF will not have this effect (Figure 1).

From scientific theory to clinical trials – ELITE-II

The theory that ARBs might be a more efficacious (blocking non-ACE-generated Ang II) and better tolerated (no kininase II inhibition) alternative to ACE-I was definitively tested in the second Evaluation of Losartan In the Elderly (ELITE-II) trial.[8,9] This study compared losartan, 50 mg once-daily, to captopril, 50 mg three times daily, in 3152 patients with NYHA Class II-IV CHF (Table 1). Despite being better tolerated, losartan was **not** more efficacious than captopril (Table 2).[9] ELITE-II was neither designed nor powered to test for equivalence (losartan as good as captopril) or non-inferiority (losartan no worse than captopril).[17] ELITE-II, therefore, tells us that ARBs should not replace ACE-I as an alternative means of suppressing the RAAS in CHF. There is, however, some concern that the dose of losartan

Figure 1 Effects of ACE inhibition and angiotensin II type 1 receptor blockade on angiotensin receptor stimulation



X = blockade; ±, +, ++, +++ = increasing degrees of receptor stimulation; - = no receptor stimulation

Table 1 Clinical characteristics of patients enrolled in ELITE-II and Val-HeFT.

	ELITE-II	Val-HeFT
Number of patients	3152	5010
Mean age (yr)	71	63
Males (%)	70	80
NYHA Class (%)		
II	52	62
III	43	36
IV	5	2
LVEF (%)	31	27
Concomitant diagnoses (%)		
Coronary aetiology*	79	57
Hypertension	49	-
Atrial fibrillation	30	-
Diabetes mellitus	24	12
Drug treatment (%)		
Diuretic	78	86
ACE inhibitor	-**	93
Cardiac glycoside	50	67
Beta-blocker	22	34

* 'history of ischaemia' in ELITE-II
** patients randomised to either losartan or captopril (23% of patients had received prior ACE inhibitor)

and dosing frequency, may not have been sufficient to adequately block the RAAS in this trial.

Combination therapy rather than alternative therapy?

The second definitive clinical trial with an ARB in CHF adopted the 'add-on' rather than 'alternative' strategy.[12] In the Valsartan Heart Failure Trial (Val-HeFT), 5010 patients with NYHA Class II-IV CHF (Table 1) were randomised to receive either placebo or valsartan, (target dose 160 mg twice-daily), in addition to background therapy. 93% of patients were taking an ACE-I and 34% a beta-blocker (Table 1). The co-primary endpoints were all-cause mortality and a mortality/morbidity endpoint (hospitalisation for CHF, resuscitated sudden death, administration of intravenous vasodilator or inotropic therapy for CHF for ≥4 hours). The results of Val-HeFT are shown in Table 3 (presented by Professor Jay Cohn at the 50th Scientific Session of the American College of Cardiology, Orlando, Florida, March, 2001). All-cause mortality was not different between groups; there was, however, a relative risk reduction in the combined mortality/morbidity endpoint of approximately 13% (p=0.009) in the valsartan group. This was mainly because of a 27% reduction in the risk of CHF hospitalisation (p=0.00001). There were also significant improvements in other secondary endpoints, such as quality of life, signs and symptoms and left ventricular ejection fraction, in the valsartan group.

At face value, Val-HeFT, therefore, seems to be a 'positive' trial. However, two subgroup analyses have probably made this interpretation too simplistic. Firstly, a very large (45%) reduction in mortality/morbidity in the small (7%) subset of patients not taking an ACE-I at baseline has led some to question whether most of the benefit in the overall Val-HeFT study population was confined to this group. Secondly, there was a trend towards an increased rate of mortality/morbidity events in the beta-blocker subgroup of patients given valsartan. Further analysis suggests that this effect was most clearly observed in patients taking both an ACE-I and beta-blocker at baseline (Figure 2). Clearly, as beta-blockers, along with ACE-I, are now recommended first line therapy for all patients with CHF, this finding is of great concern.

It must be emphasised, however, that retrospective subgroup analysis of this type can be very misleading.[18] Often, apparent differences in response merely reflect the small numbers of patients in certain subsets and the play of chance. Proper interpretation requires assessment of internal and external consistency and biological plausibility. The first of these is impossible as the full data (e.g. on left ventricular remodelling, neurohumoral responses, etc.) are not available. There is conflicting evidence when it comes to external consistency. A directionally similar interaction with beta-blockers was noted in ELITE-II. No concerns, however, have been raised in relation to the very large, on-going valsartan in acute myocardial infarction trial (VALIANT), in which patients are randomised to valsartan, captopril or their combination and where more than 70% are taking a beta-blocker.[19]

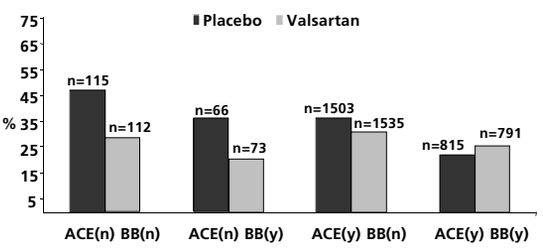
Table 2 ELITE-II endpoints.

Endpoint	Number of patients		HR (95%CI)	p-value
	Losartan n=1578	Captopril n=1574		
All-cause mortality	280 (17.7%)	250 (15.9%)	1.13 (0.95–1.35)	0.16
Sudden death or resuscitated cardiac arrest	142 (9.0%)	115 (7.3%)	1.25 (0.98–1.60)	0.08
Combined total mortality or hospitalisation for any reason	752 (47.7%)	707 (44.9%)	1.07 (0.97–1.19)	0.18
Hospital admissions (all-causes)	659 (41.8%)	638 (40.5%)	1.04 (0.94–1.16)	0.45

Table 3 Val-HeFT: endpoints.

Endpoint	Number of patients		RR (95% CI)	p-value
	Valsartan n=2511	Placebo n=2499		
All-cause mortality	495 (19.7%)	484 (19.4%)	1.02 (0.90, 1.15)	0.800
Combined all-cause mortality + morbidity	723 (28.8%)	801 (32.1%)	0.87 (0.79, 0.96)	0.009
HF hospitalisations	349 (13.9%)	463 (18.5%)	0.73 (0.63, 0.83)	0.00001

Figure 2 Combined all-cause mortality and morbidity ACE inhibitor/beta-blocker subgroups.



n = no; y = yes

There is also no good, biologically plausible explanation for an adverse interaction between beta-blockers and ARBs (or the combination of beta-blockers and ACE-I and an ARB).

What is the place of ARBs in the management of CHF after ELITE-II and Val-HeFT?

The totality of the currently available evidence suggests that ARBs may be a useful alternative to ACE-I in patients intolerant of the latter. This assumption is, however, being formally tested in one arm of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) programme.[20]

ARBs are not a general alternative to ACE-I, which remain first line therapy for all patients with CHF who can tolerate them.

The more difficult question is whether to recommend an ARB in addition to an ACE-I? Presently, in patients taking a beta-blocker (and that should be most patients) this is not advisable. Again, however, the CHARM programme, which has an ACE-I/ARB combination arm (in which around half of patients are receiving a beta-blocker), and VALIANT trial will give more information on this issue in the next two to three years.[19,20] In patients not taking a beta-blocker, adding an ARB to background ACE-I treatment seems an acceptable strategy. The last and hardest of all scenarios to judge is that where the patient cannot take an ACE-I but can take a beta-blocker. Should such a patient receive an ARB as well as a beta-blocker? The subgroup analysis shown in Figure 2 suggests 'yes' but the most cautious interpretation of the beta-blocker/ARB interaction question would say 'wait for CHARM and VALIANT to finish and just use a beta-blocker at present'.

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