

심부전의 치료에서 안지오텐신 수용체 차단제의 역할

전 은 석

Role of Angiotensin II Receptor Blockers in the Treatment of Congestive Heart Failure

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ABSTRACT

Pharmacotherapy for the treatment of heart failure has advanced considerably in recent years, and clinical trials have demonstrated the favorable long-term effects of angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers on the morbidity and mortality. Although the current guidelines recommend ACEI and beta-blockers as standard therapy for heart failure, as they have demonstrated benefits in terms of mortality, only one third of patients with heart failure are receiving both classes of drug due to concern over their adverse effects. The benefit of ACEI has been attributed largely to blockade of angiotensin II production, but also to the accumulation of bradykinin. The accumulation of bradykinin however, has been implicated as contributing to adverse effects, such as a dry cough, associated with ACEI treatment, and has also been suggested to result in prejunctional norepinephrine release. Recently, many clinical trials have shown that angiotensin receptor blockers (ARBs) had similar effect on the mortality and morbidity of patients with heart failure. The side effects, notably the cough, are significantly less than with ACE inhibitors. ARBs could also be recommended for patients who can not tolerate ACE inhibitors for symptomatic treatment. In combination with ACEI, ARBs may improve the symptoms of heart failure, and reduce hospitalizations due to heart failure deterioration. Whether concomitant beta-blockade negatively affects the effect of ARB will require further evaluation. In this paper, recent large clinical trials of ARBs therapy in heart failure, and the ongoing clinical trials, were reviewed for the recommendation of the optimal conditions for ARBs treatment in heart failures. (**Korean Circulation J 2002;32(12):1039-1045**)

KEY WORDS : Heart failure, congestive ; Angiotensin II receptor ; Angiotensin-converting enzyme inhibitors.

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. 1999~2000

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(, , 33~36%), (22~23%)
가 , (19~22%), (13~15%)
. 1950 1980

본 론

uroendocrine activation) (neurohumoral hypothesis) (cytokine) (angiotensin converting enzyme inhibitor ; ACEI) Captopril enalapril, lisinopril

1980 65

가 (neurohumoral hypothesis) ACEI captopril ARB losartan

(angiotensin converting enzyme inhibitor ; ACEI) York Heart Association(NYHA) Class II IV

, Captopril enalapril, lisinopril ACEI

40% losartan (50 mg , n=352) captopril (50 mg 3 , n=370) 48

30~40% 0.3 mg/dl

ACEI 가 (angiotensin II receptor blocker : ARB) 가

가

가

ARB가 ACEI 352), captopril 29.7%(110/370)

가

ARB losartan 9.4%, captopril 13.2% 68%

(p =

Table 1. Deaths and causes of death and admission for heart failure or for any reason in ELITE I trial

Endpoint	Losartan (n = 352)	Captopril (n = 370)	Risk reduction (CI)*	p†
Combined death and/or hospital admission for heart failure	33 (9.4%)	49 (13.2%)	0.32 (- 0.04 to + 0.55)	0.075
All deaths	17 (4.8%)	32 (8.7%)	0.46 (0.05 - 0.69)	0.035
Cardiovascular				
Sudden death	57 (1.4%)	14 (3.8%)	0.64 (0.03 - 0.86)	
Progressive heart failure	1	1	- 0.11 (- 20.23 to + 0.94)	
Myocardial infarction	1	4 (1.1%)	0.76 (- 0.83 to + 0.97)	
Other vascular	5 (1.4%)	5 (1.4%)	- 0.03 (- 2.63 to + 0.71)	
Non-cardiovascular	5 (1.4%)	8 (2.2%)	0.35 (- 0.94 to + 0.78)	
Hospital admissions				
For heart failure	20 (5.7%)	21 (5.7%)	0.04 (- 0.74 to + 0.47)	0.89
For any reason	78 (22.2%)	110 (29.7%)	0.26 (0.05 - 0.43)	0.014

* : reduced risk of endpoint on losartan compared with captopril (negative number denotes increase in risk) ; estimates control for age category ; CI = 95% confidence interval, † : log-rank test (survival analysis) with age category included as stratification factor

0.075). losartan 4.8%,
 captopril 8.7% (p=0.035) 가 (p<0.01),
 losartan 36% (p<0.05).
 17
 losartan 22.2%, captopril (p<0.05), B
 29.7% 74% (p= (B-type natriuretic peptide) 17, 43
 0.014) (Table 1). losartan (p<0.01).
 captopril, 3,
 가 lo-
 sartan captopril (Table 2) ARB ACEI
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RESOLVED(Randomized Evaluation of Strategies for Left Ventricular Dysfunction) 연구²⁾ ELITE II 연구³⁾
 NYHA Class II - IV ELITE I 60
 NYHA Class II - IV
 candesartan (16 mg, n=327), 40% 3,152
 candesartan, enalapril (candesartan losartan (50 mg, n=
 4 8 mg, enalapril 10 mg 2, 1,578) captopril (50 mg 3
 n=332), enalapril (10 mg 2, n=1,574) 1.5
 , n=109) 43
 17~18 43 6 (6-minute (resuscitated cardiac arrest)
 walking distance),
 , NYHA functional class
 ELITE I losar-
 tan captopril 가

Table 2. Clinical events up to week 43 in RESOLVD trial

	Candesartan				Combination*				Enalapril
	Total group	4 mg	8 mg	16 mg	Total group	4 mg	8 mg	20 mg	p [†]
	(n = 327), n (%)	(n = 111), n (%)	(n = 108), n (%)	(n = 108), n (%)	(n = 332), n (%)	(n = 165), n (%)	(n = 167), n (%)	(n = 109), n (%)	
Death	20 (6.1)	7 (6.3)	8 (7.4)	5 (4.6)	29 (8.7)	10 (6.1)	19 (11.4)	4 (3.7)	0.15
Any CHF hospitalization	43 (13.1)	11 (9.9)	20 (18.5)	12 (11.1)	31 (9.3)	18 (10.9)	13 (7.8)	7 (6.4)	0.09
Any hospitalization	87 (26.6)	22 (19.8)	37 (34.3)	28 (25.9)	80 (24.1)	42 (25.5)	38 (22.8)	24 (22.0)	0.58
Death/any CHF hospitalization	55 (16.8)	17 (15.3)	22 (20.4)	16 (14.8)	58 (17.5)	27 (16.4)	31 (18.6)	10 (9.2)	0.11
Death/any hospitalization	96 (29.4)	27 (24.3)	38 (35.2)	31 (28.7)	102 (30.7)	48 (29.1)	54 (32.3)	26 (23.9)	0.39
Renal dysfunction	2 (0.6)	1 (0.9)	1 (0.9)	0 (0)	2 (0.6)	0 (0)	2 (1.2)	0 (0)	0.72
Symptomatic hypotension	3 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	4 (1.2)	1 (0.6)	3 (1.8)	1 (0.9)	0.93

* : combination includes enalapril 20 mg daily with the candesartan dose, † : based on a ² comparison across the total in the 3 main groups of candesartan, combination, and enalapril. Of the 10 pairwise comparisons of candesartan alone vs enalapril or the combination group vs enalapril, none were statistically significant except for the outcome of death/any CHF hospitalization between combination vs enalapril (p=0.037). CHF : congestive heart failure

Table 3. Endpoint results in ELITE II trial

Endpoint	Losartan (n = 1578)	Captopril (n = 1574)	Hazards ratio (CI)*	p
All-cause mortality (primary endpoint)				
Total mortality	280 (17.7%)	250 (15.9%)	1.13 (0.95 - 1.35)	0.16
Sudden death	130 (8.2%)	101 (6.4%)	1.30 (1.00 - 1.69)	
Progressive heart failure	46 (2.9%)	53 (3.4%)	0.88 (0.59 - 1.30)	
Myocardial infarction	31 (2.0%)	28 (1.8%)	1.11 (0.66 - 1.85)	
Stroke	18 (1.1%)	11 (0.7%)	1.65 (0.78 - 3.49)	
Other cardiovascular	5 (0.3%)	6 (0.4%)	0.84 (0.26 - 2.76)	
Non-cardiovascular	50 (3.2%)	51 (3.2%)	0.99 (0.67 - 1.47)	
Sudden death or resuscitated cardiac arrest	142 (9.0%)	115 (7.3%)	1.25 (0.98 - 1.60)	0.08
Combined total mortality or hospital admission for any reason	752 (47.7%)	707 (44.9%)	1.07 (0.97 - 1.19)	0.18
Hospital admissions				
Any reason	659 (41.8%)	638 (40.5%)	1.04 (0.94 - 1.16)	0.45
Heart failure	270 (17.1%)	293 (18.6%)	0.92 (0.78 - 1.08)	0.32

* : 95.7% CI for total mortality, 95% CI for other endpoints, including components

Table 4. Incidence and relative risk of the primary endpoints in Val-HeFT study

Event	Valsartan group (n = 2511)	Placebo group (n = 2499)	Relative risk (CI)*	p†
	vasaltau plaabe no. with event			
Death from any cause (during entire trial)	495 (19.7)	484 (19.4)	1.02 (0.88 - 1.18)	0.80
Combined end point	723 (28.8)	801 (32.1)	0.87 (0.77 - 0.97)	0.009
Death from any cause (as first event)	356 (14.2)	315 (12.6)		
Hospitalization for heart failure	346 (13.8)	455 (18.2)		
Cardiac arrest with resuscitation	16 (0.6)	26 (1.0)		
Intravenous therapy	5 (0.2)	5 (0.2)		

* : the 98 percent confidence interval (CI) was calculated for the mortality end point (death from any cause), and the 97.5 percent confidence interval was calculated for the combined mortality-morbidity end point, † p were calculated by the log-rank test from time to first event

가 captopril (7.3%) Val-HeFT(Valsartan Heart Failure Trial) 연구⁴⁾
losartan (9.0%) ARB valsartan
(p = 0.08). . 18
3 5,011 Val-
가 (Table 3). sartan (160 mg 2 , n =
losartan 2511) (n = 2499) 23
. ,
가 가 losartan (, ,
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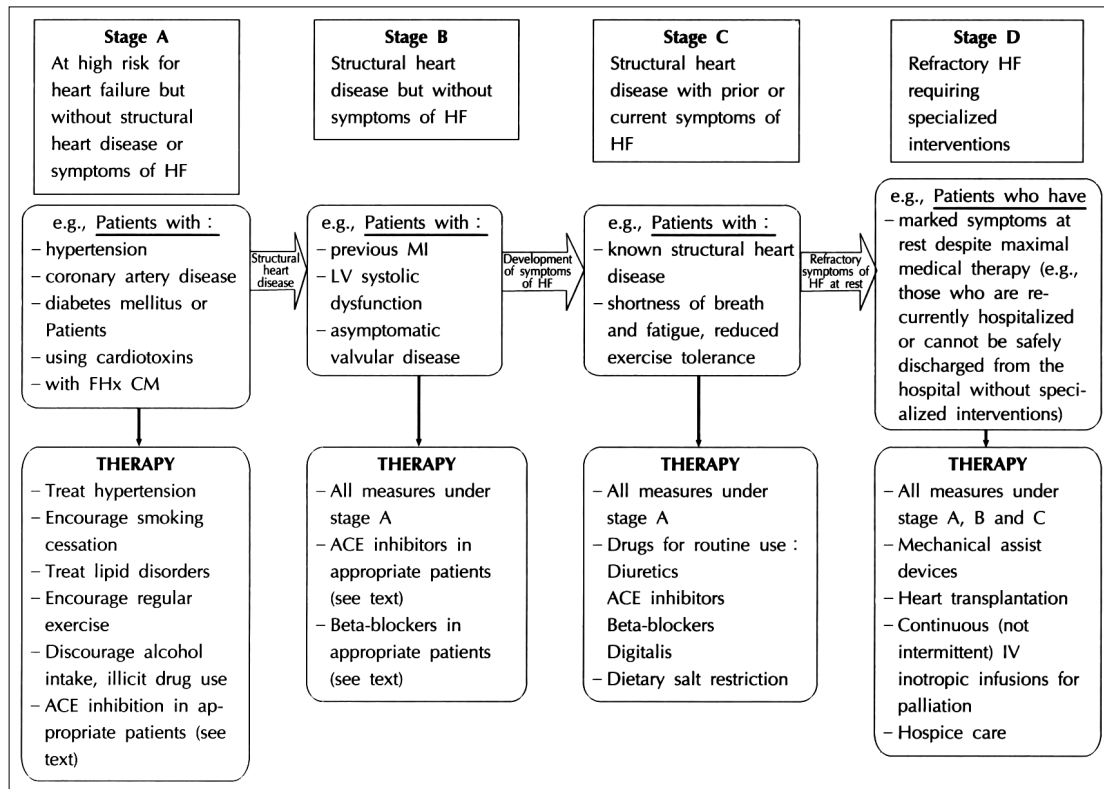


Fig. 1. Stages in the evolution of HF and recommended therapy by stage. FHx CM indicates family history of cardiomyopathy. MI : myocardial infarction, LV : left ventricular, and IV : intravenous (in AHA/ACC guideline).

	For Symptoms	For Survival/Morbidity <i>mandatory therapy</i>	For Symptoms if Intolerance to ACE inhibition or Betablockade
NYHA I	reduce / stop diuretic	continue ACE inhibitor if asymptomatic	
NYHA II	↑ +/- diuretic depending on fluid retention	ACE inhibitor as first-line treatment ↓ add beta-blocker if still symptomatic	ARB if ACE inhibitor intolerant or ACE inhibitor+ARB if beta-blocker intolerant
NYHA III	+ diuretics+ digitalis if still symptomatic + nitrates/hydralazine if tolerated	ACE inhibitor and beta-blockade add spironolactone, ↓	ARB if ACE inhibitor intolerant or ACE inhibitor+ARB if beta-blocker intolerant
NYHA IV	diuretics+ digitalis + nitrates/hydralazine if tolerated + temporary inotropic support	ACE inhibitor beta-blockade spironolactone	ARB if ACE inhibitor intolerant or ACE inhibitor+ARB if beta-blocker intolerant

Fig. 2. Pharmacological therapy of symptomatic chronic heart failure due to systolic left ventricular dysfunction (in ESC guideline). NYHA : New York heart association, ACE : angiotensin converting enzyme, ARB : angiotensin II receptor blockers.

(p=0.009). valsartan 13.8%, 18.2% (Table 4). ACEI가 90% 1/3 ELITE I, II ARB ACEI ACEI 가 valsartan 심부전의 치료에 대한 AHA/ACC 및 ESC 치료지침에서 ARB의 역할 2001 AHA/ACC ESC 5) 2002 ARB ACEI (Fig. 1, 2). ELITE I, II, RE-SOLVD ARB 가

CHARM(Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity)⁷⁾ 가 VALIANT(Valsartan in Acute Myocardial Infarction Trial)⁸⁾

결론

, ARB ACEI ACEI ARB 2 ARB

, val-sartan , losartan 가 , ARB가 1 가 . RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan)⁹⁾ LIFE (Losartan Intervention For Endpoint reduction in hypertension study)¹⁰⁾ losartan 100 mg ELITE II 3) OPTIMAAL(Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan)¹¹⁾ losartan 50 mg - 가 , HEAAL(Heart failure End-point evaluation with the Angiotensin II Antagonist Losartan) losartan 50 mg 150 mg 가 , ARB 가 ARB 1 가 . 중심 단어 : ; ;

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