

# 이첨판 폐쇄부전 환자(N=166)에 Entresto 적용과 고찰

2024.1.07

부천비엔동물전문의료센터

양명환

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# 목 차

**이첨판 폐쇄부전, 그리고 RAAS**

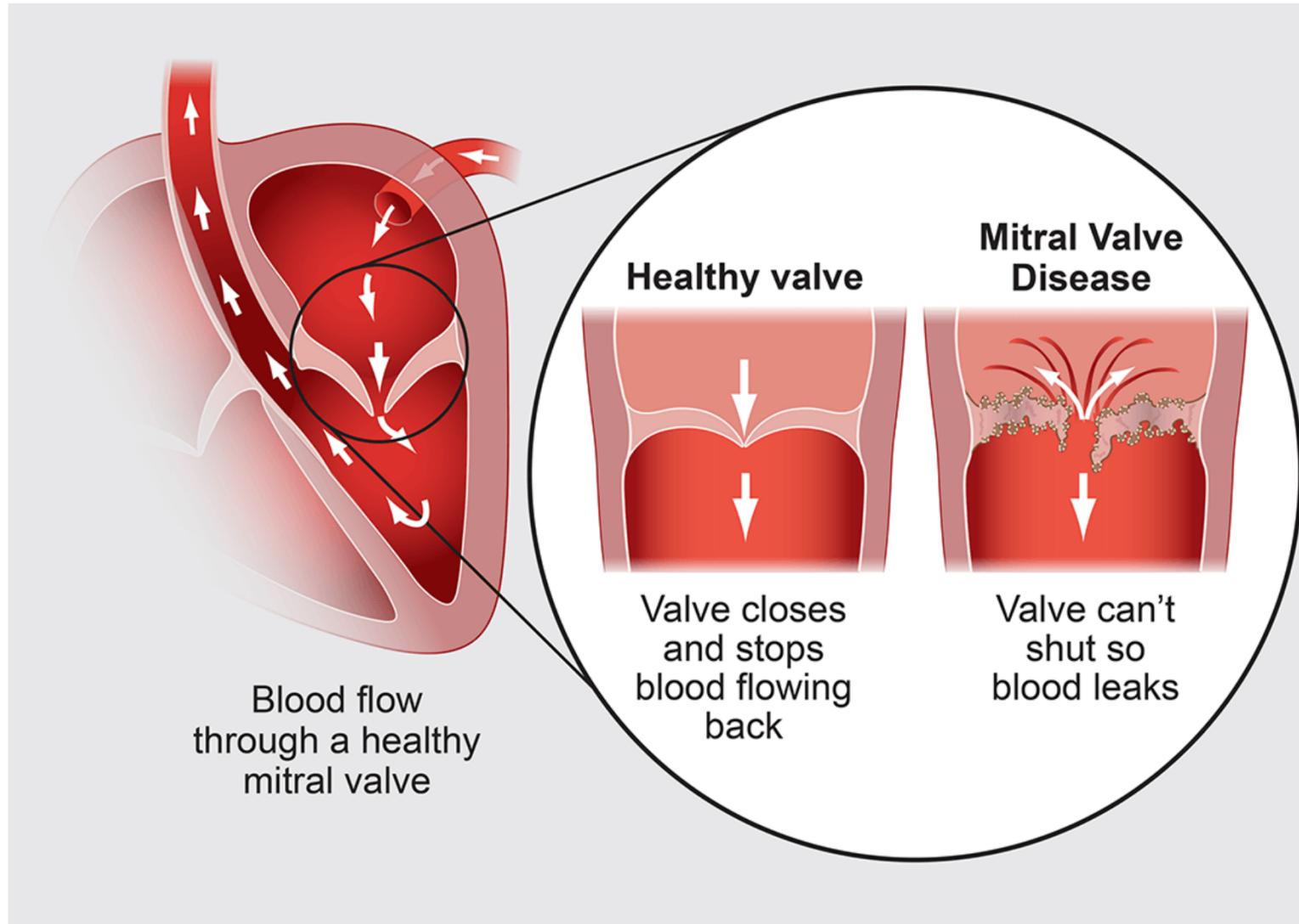
**Entresto(ARNi) 란?**

**Entresto -MMVD환자에 투약 후 회고적 평가**

**결론**

**이첨판 폐쇄부전, 그리고 RAAS**

# 강아지 이첨판 폐쇄부전 (MMVD)



- 좌심실과 좌심방 사이의 판막변성으로 심기능의 저하를 유발하는 질환
- 소형견에서 흔하게 발생

# 강아지 이첨판 폐쇄부전 (MMVD)

이첨판 폐쇄부전, 그리고 RAAS

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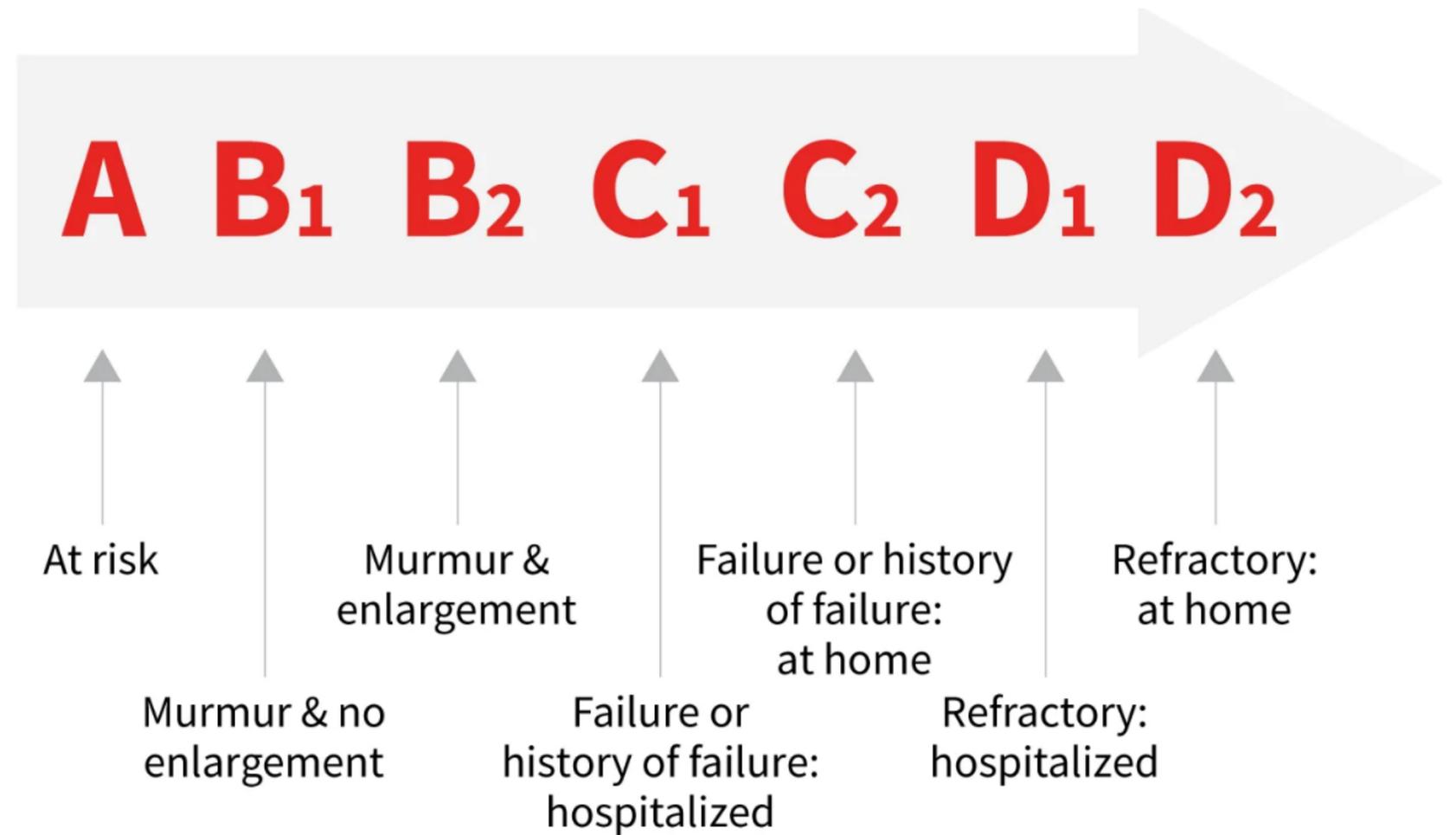
## CONSENSUS STATEMENT



Consensus Statements of the American College of Veterinary Internal Medicine (ACVIM) provide the veterinary community with up-to-date information on the pathophysiology, diagnosis, and treatment of clinically important animal diseases. The ACVIM Board of Regents oversees selection of relevant topics, identification of panel members with the expertise to draft the statements, and other aspects of assuring the integrity of the process. The statements are derived from evidence-based medicine whenever possible and the panel offers interpretive comments when such evidence is inadequate or contradictory. A draft is prepared by the panel, followed by solicitation of input by the ACVIM membership which may be incorporated into the statement. It is then submitted to the *Journal of Veterinary Internal Medicine*, where it is edited prior to publication. The authors are solely responsible for the content of the statements.

## ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs

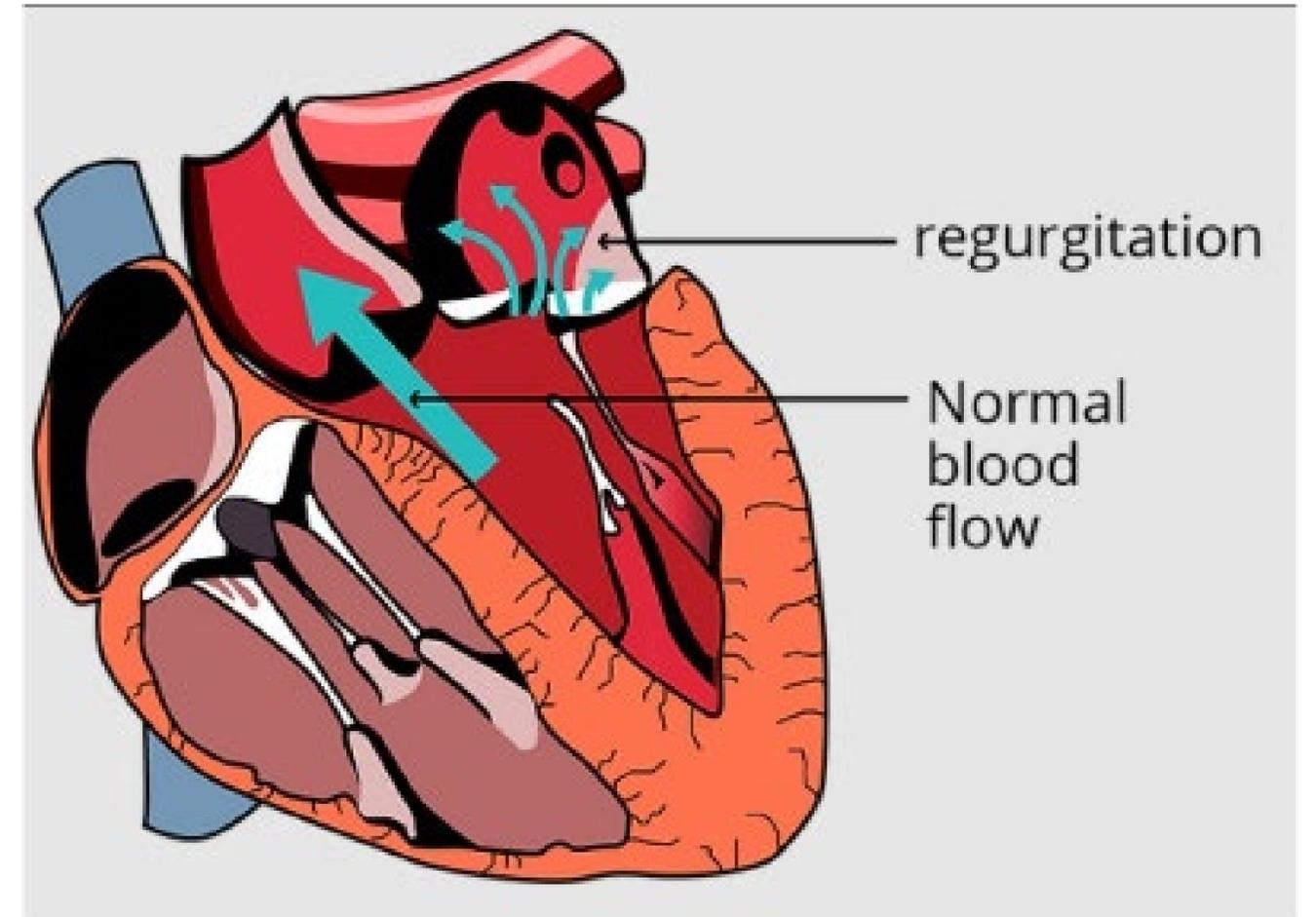
Bruce W. Keene<sup>1</sup> | Clarke E. Atkins<sup>1</sup> | John D. Bonagura<sup>1,2</sup> | Philip R. Fox<sup>3</sup> |  
Jens Häggström<sup>4</sup> | Virginia Luis Fuentes<sup>5</sup> | Mark A. Oyama<sup>6</sup> | John E. Rush<sup>7</sup> |  
Rebecca Stepien<sup>8</sup> | Masami Uechi<sup>9</sup>



# 강아지 이첨판 폐쇄부전 (MMVD)

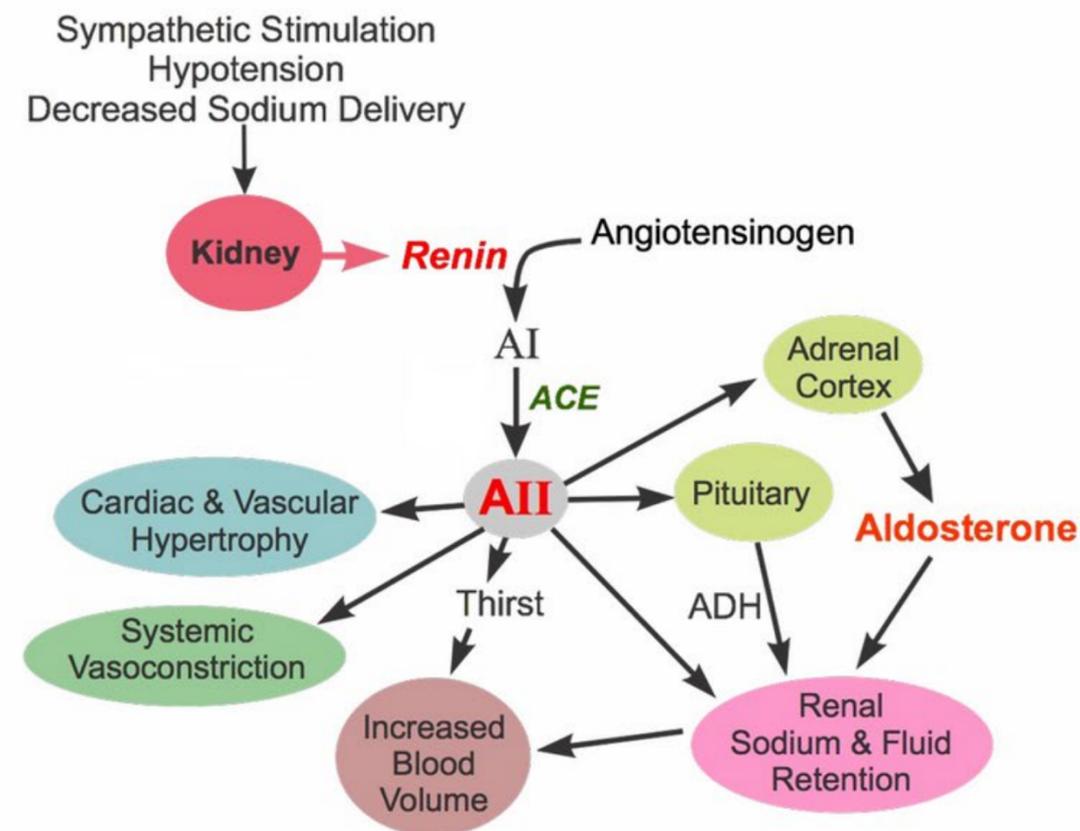
이첨판 폐쇄부전, 그리고 RAAS

- 역류로 인해 정상적으로 이동하는 혈류는 감소



# 강아지 이첨판 폐쇄부전 (MMVD)

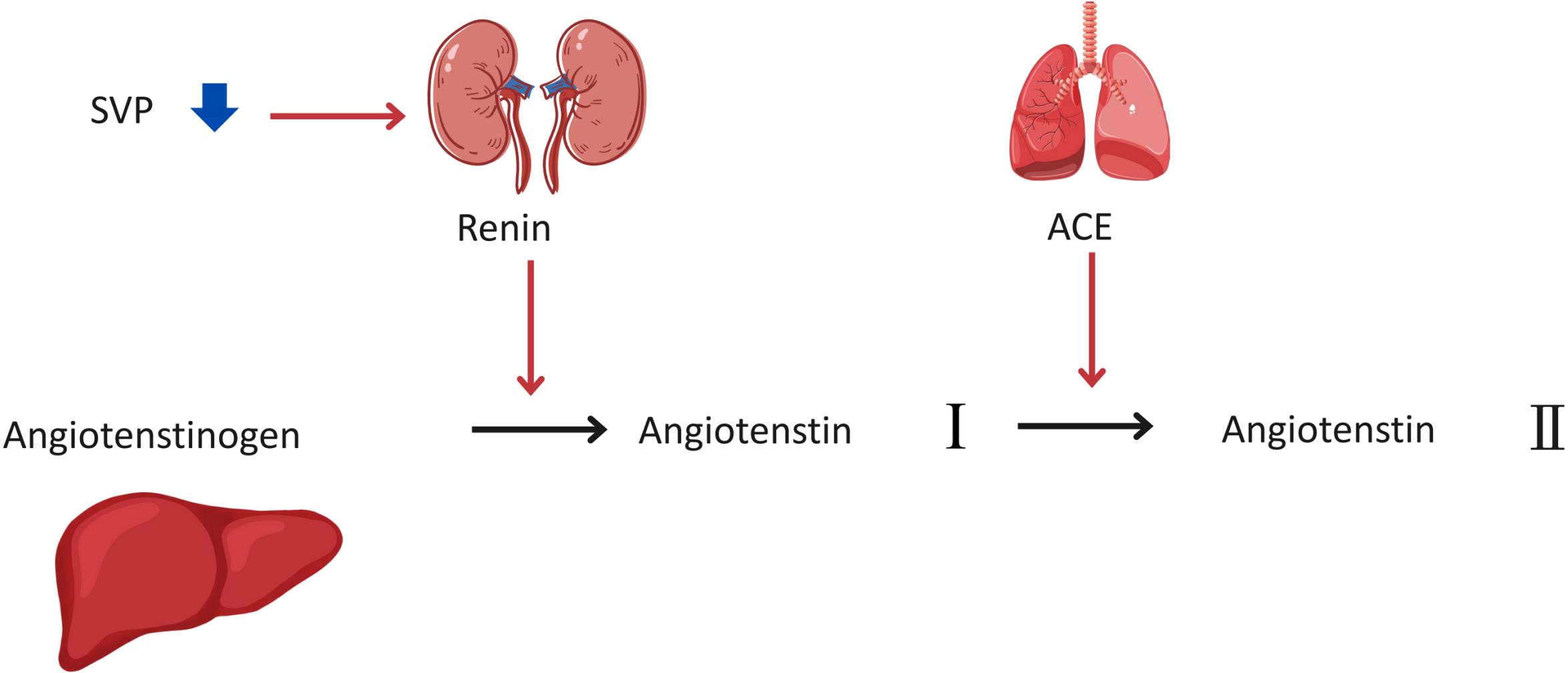
- 이때 순환 혈류량의 감소는 Renin angiotensin aldosterone system을 항진시킨다.



• Renin angiotensin aldosterone system - 이하 RAAS 의 모식도

# RAAS(Renin Angiotensin Aldosteron System)

- 신체의 전신 혈압을 유지하기 위한 호르몬 시스템

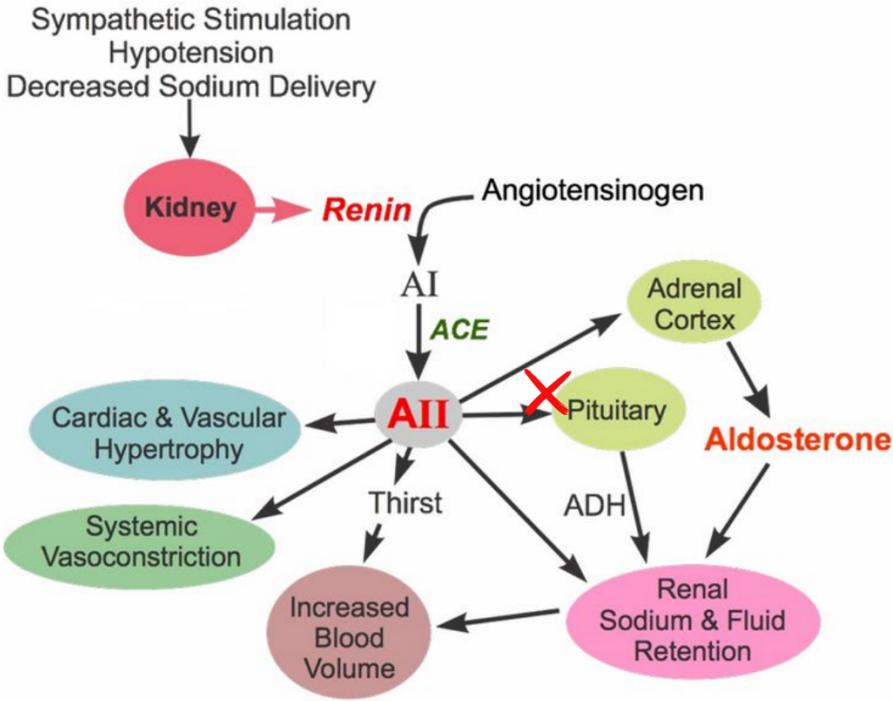


# RAAS(Renin Angiotensin Aldosteron System)

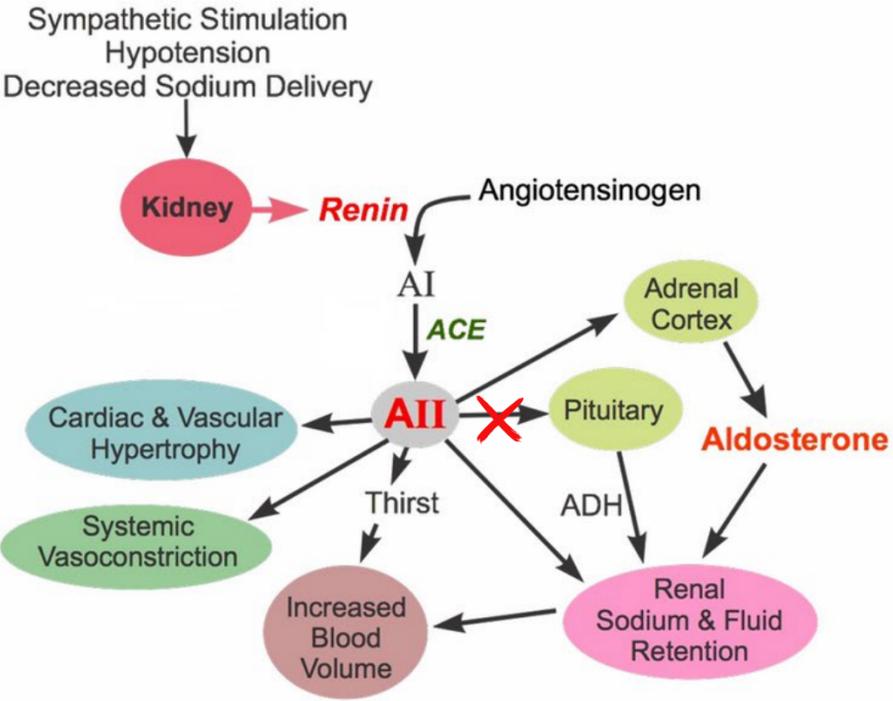
- Angiotenstin II 활성화



# Classic RAAS 차단제



ACE inhibitor



ARB(Angiotensin receptor blocker)

### Aldosterone breakthrough in dogs with naturally occurring myxomatous mitral valve disease.

Language: English

J Vet Cardiol. June 2017;19(3):218-227.

M K Ames<sup>1</sup>, C E Atkins<sup>2</sup>, A Eriksson<sup>2</sup>, A M Hess<sup>3</sup>

[Display author information](#)

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### Results

The prevalence of ABT was 32% in dogs with CHF and 30% in dogs without CHF. There was no relationship between either the UAldo:C or the likelihood of ABT and the eight variables. Therapy with spironolactone lead to a significant elevation of the UAldo:C.

### Discussion

Using the UAldo:C and a relatively stringent definition of ABT, it appears that incomplete RAAS blockade is common in dogs with MMVD receiving an ACEI. The prevalence of ABT in this canine population mirrors that reported in humans. While the mechanism of ABT is likely multifactorial and still poorly understood, the proven existence of ABT in dogs offers the potential to improve the prognosis for MMVD with the addition of a mineralocorticoid receptor blocker to current therapeutic regimens.

### Conclusions

Approximately 30% of dogs being treated for heart disease and CHF satisfied the definition of ABT. Identifying patient subpopulations experiencing ABT may help guide future study design and clinical decision-making.

\* 라스차단제들의 한계점..

1. aldosteron breakthrough
2. Bradikinin 의 분해 억제
3. MMVD 환자에서 효능에 대한 의문

- 충분히 억제하는가? 어디를 차단해야 가장 효과적인가..  
에 대한 실험

**Entresto(ARNi) 란?**

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# Paradigm heart failure

**RAAS 의 어디를 얼마만큼 차단해야 하나?**

**심부전에 유의미한 생존률 차이를 보이나요?**

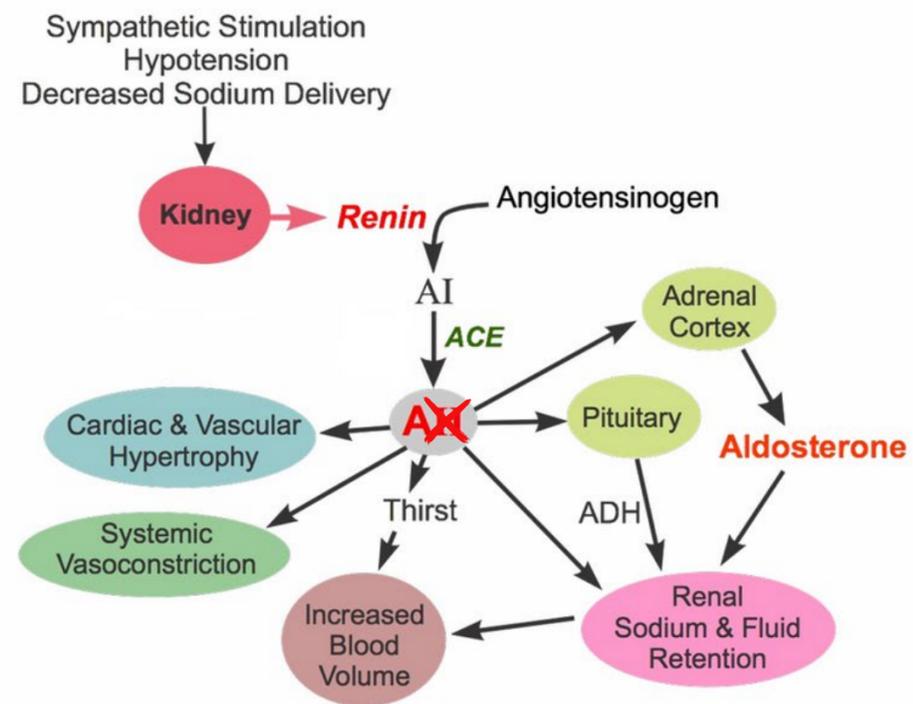
**기존의 약제보다 우월한 효과가 있는가?**

# Entresto(ARNi)기전

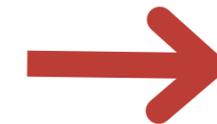
Valsartan(ARB)

+

Sacubitril(Nephrylisin inhibitor)



Nephrylisin



BNP

ARB(Angiotensin receptor blocker)

# Paradigm heart failure

## PARADIGM-HF versus ATMOSPHERE

(대상: Heart Failure with Reduced EF)



**15,415 patients. NYHA class II-IV, LVEF  $\leq$ 40% (35%),**

BNP  $\geq$ 150 pg/ml or NT pro-BNP  $\geq$ 600 pg/ml;  
or if hospitalized in past 12 months BNP  $\geq$ 100 pg/ml or NT proBNP  $\geq$  400 pg/ml

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 37

Angiotensin–Nepriylsin Inhibition versus Enalapril  
in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D.,  
Martin P. Leffowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D.,  
Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D.,  
for the PARADIGM-HF Investigators and Committees\*

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N Engl J Med 2016;374:1521-32

Aliskiren, Enalapril, or Aliskiren and  
Enalapril in Heart Failure

John J.V. McMurray, M.D., Henry Krum, M.B., B.S., Ph.D.,<sup>†</sup> William T. Abraham, M.D.,  
Kenneth Dickstein, M.D., Ph.D., Lars V. Kober, M.D., D.M.Sc.,  
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M. Atif Ali, B.A., Yanntong Chiang, Ph.D., Qing Shao, Ph.D.,  
Georgia Tarnesby, M.B., B.Chir., and Barry M. Massie, M.D.,  
for the ATMOSPHERE Committees Investigators†

**Enrollment criteria: Stable (4주 이상) ACE inhibitor or ARB at dose  $\geq$   
enalapril 10 mg daily +  $\beta$ blocker + aldosterone antagonist (as indicated)**

## RESULTS

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87;  $P < 0.001$ ). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93;  $P < 0.001$ ); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89;  $P < 0.001$ ). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% ( $P < 0.001$ ) and decreased the symptoms and physical limitations of heart failure ( $P = 0.001$ ). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

# Paradigm heart failure

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CARDIOLOGY FOUNDATION, AND THE HEART FAILURE SOCIETY OF AMERICA.  
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## CLINICAL PRACTICE GUIDELINE: FULL TEXT

### 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure



A Report of the American College of Cardiology/American Heart Association  
Joint Committee on Clinical Practice Guidelines

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‡ACC/AHA Representative. †ACC/AHA Joint Committee on Clinical  
Practice Guidelines Liaison. §ACC/AHA Task Force on Performance  
Measures Representative. ||HFSA Representative.

## HFrEF: The 2022 HF Guideline recommends ENTRESTO to reduce morbidity and mortality<sup>‡</sup>

\*In PARAGON-HF, defined as LVEF  $\geq$ 45% with structural heart disease (LAE or LVH); median LVEF was 57%. LVEF is a variable measure and the normal range can vary.<sup>2</sup>

†In the 2022 HF Guideline, ENTRESTO is recommended as a first-line treatment and to replace well-tolerated ACEi/ARB in patients with NYHA Class II–III HFrEF (Class 1 recommendation). ENTRESTO was also included as a treatment option for HFmrEF (LVEF 41%–49%) and select patients with HFpEF (LVEF  $\geq$ 50%), particularly for patients with LVEF on the lower end of the spectrum (Class 2b recommendation).

‡NYHA Class II–III patients with HFrEF.

### Class 1 recommendation to **REPLACE ACEi/ARB**<sup>1§</sup>

§In NYHA Class II–III HFrEF in patients who tolerate ACEi/ARB.

# MMVD 환자에서 Entresto 투여?

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DOI: 10.1111/jvim.15240

Journal of Veterinary Internal Medicine   
Open Access American College of  
Veterinary Internal Medicine

## STANDARD ARTICLE

### A prospective, randomized, double-blind, placebo-controlled pilot study of sacubitril/valsartan (Entresto) in dogs with cardiomegaly secondary to myxomatous mitral valve disease

Daniel K. Newhard | SeungWoo Jung  | Randolph L. Winter | Sue H. Duran

**Results:** Thirteen dogs were recruited: S/V (n = 7) and placebo (n = 6). The median percentage increase in urinary aldosterone to creatinine ratio (UAldo : C) between day 0 and day 30 was significantly lower in the S/V group (12%; P = .032) as compared with the placebo group (195%). The median percentage decrease of NT-proBNP concentration from day 0 to day 30 was not statistically different between groups (P = .68). No statistical differences were seen in echocardiographic, thoracic radiographic, SAP, or serum biochemical test results measured at any time point between groups. No adverse events were observed for dogs in either group.

**Conclusion and clinical importance:** Sacubitril/valsartan may provide a new pharmaceutical method to effectively inhibit the RAAS in dogs with ACVIM Stage B2 MMVD.

MMVD b2 환자에서 투여

placebo 군 = acei 투여

Entresto 투여군과 비교

MMVD b2 환자에서 NT-Probnp

Aldosterone level을 효과적으로 낮춰줌

# MMVD 환자에서 Entresto 투여?

Entresto(ARNi) 란?



## Short-Term Effects of Sacubitril/valsartan on Echocardiographic Parameters in Dogs With Symptomatic Myxomatous Mitral Valve Disease

Nakkawee Saengklub<sup>1\*</sup>, Prapawadee Pirintr<sup>2</sup>, Thanida Nampimoon<sup>3</sup>, Anusak Kijawornrat<sup>3\*</sup> and Narongsak Chaiyabutr<sup>4</sup>

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OPEN ACCESS

**Methods:** In this prospective, randomized, single-blind study, 21 dogs with MMVD stage C were randomly assigned to received SV (20 mg/kg orally twice a day) or ramipril (0.125 mg/kg, orally once a day) in addition to pimobendan and furosemide. Echocardiography, electrocardiography, blood pressure, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and urinary aldosterone per creatinine ratio were obtained at baseline (D0) and at follow-up (4 weeks).

**Results:** When comparing the percent change from baseline between groups, the left atrium to aortic root ratio (LA/Ao) and left ventricular internal diameter diastole normalized to body weight (LVIDDN) were significantly reduced in the SV group ( $P < 0.001$  and  $P < 0.01$ , respectively). The end-diastolic volume index (EDVI), end-systolic volume index (ESVI), and stroke volume were lower in the SV group ( $P < 0.001$ ,  $P < 0.05$ , and  $P < 0.01$ , respectively). No changes were observed between groups for NTproBNP, blood pressure, ECG parameters, and urinary aldosterone per creatinine ratio.

**Conclusion:** The current study suggested that the short-term effects of SV can reverse myocardial remodeling, as inferred from several echocardiographic indices (i.e., the reduction in LA/Ao, LVIDDN, EDVI and ESVI) in dogs with MMVD stage C. These findings would support the use of SV in clinically symptomatic heart failure in dogs.

# Entresto - MMVD환자에 투약 후 회고적 평가

## 투여 기준

MMVD b2,C Acei 투여 중 신 수치 상승 혹은 빠른 LA : AO, E peak의 악화  
, 전신 고혈압 환자

- 환자들은 Acei 를 단약하며 Entresto 10mpk BID 투여

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# 평가 항목

**B2 환자에서 2주 후 NA, K, Crea, BUN, La size, Epeak 평가**

**C 환자는 이뇨제 투약용량이 변하여 Long term 투여에 대한  
안정성 평가만 진행 (회고적 평가의 한계)**

# 결과 - B2 shortterm

Entresto -MMVD환자에 투약 후 회고적 고찰

<i>N=102</i>	Day 0 (Mean ± SD)	+14~28 Day (Mean ± SD)	P-value
BUN	31.93 ± 11.17	31.16 ± 12.29	0.466
Crea	0.82 ± 0.33	0.81 ± 0.29	0.607
Na+	147.20 ± 4.82	146.69 ± 4.39	0.408
K+	4.40 ± 0.45	4.32 ± 0.48	0.169
E_peak	106.03 ± 25.76	99.29 ± 26.77	0.028
MR_PG	125.23 ± 15.59	125.65 ± 14.26	0.843
LA:Ao	1.76 ± 0.16	1.70 ± 0.18	0.003
LVIDDn	1.83 ± 0.16	1.76 ± 0.20	0.001

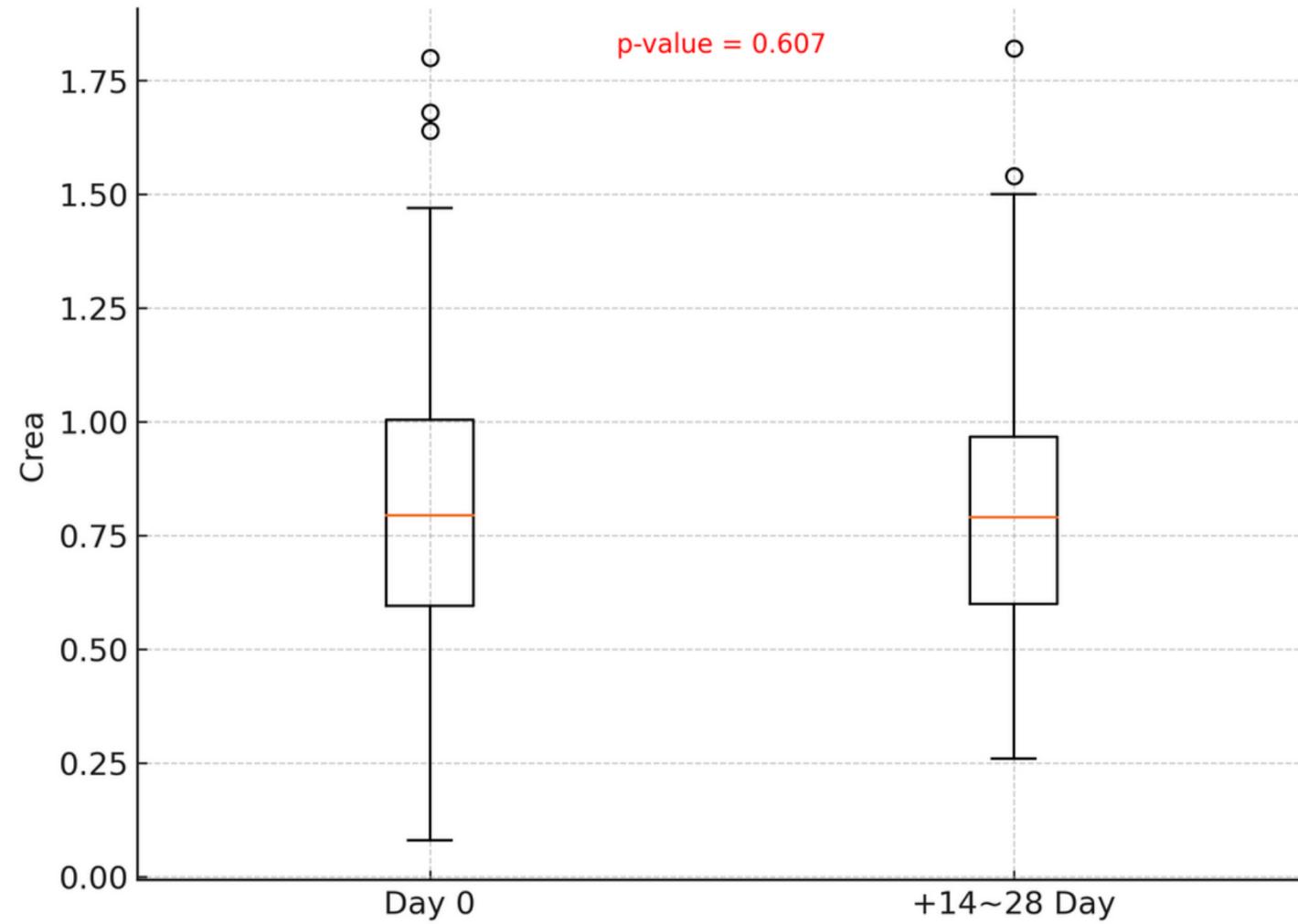
Bun(mg/dL),Crea(mg/dL), Na(mmol/L), K(mmol/L), MV E peak vel(cm/s) , MR PG(mmHg)

# 결과 - B2 shortterm

Entresto -MMVD환자에 투약 후 회고적 고찰

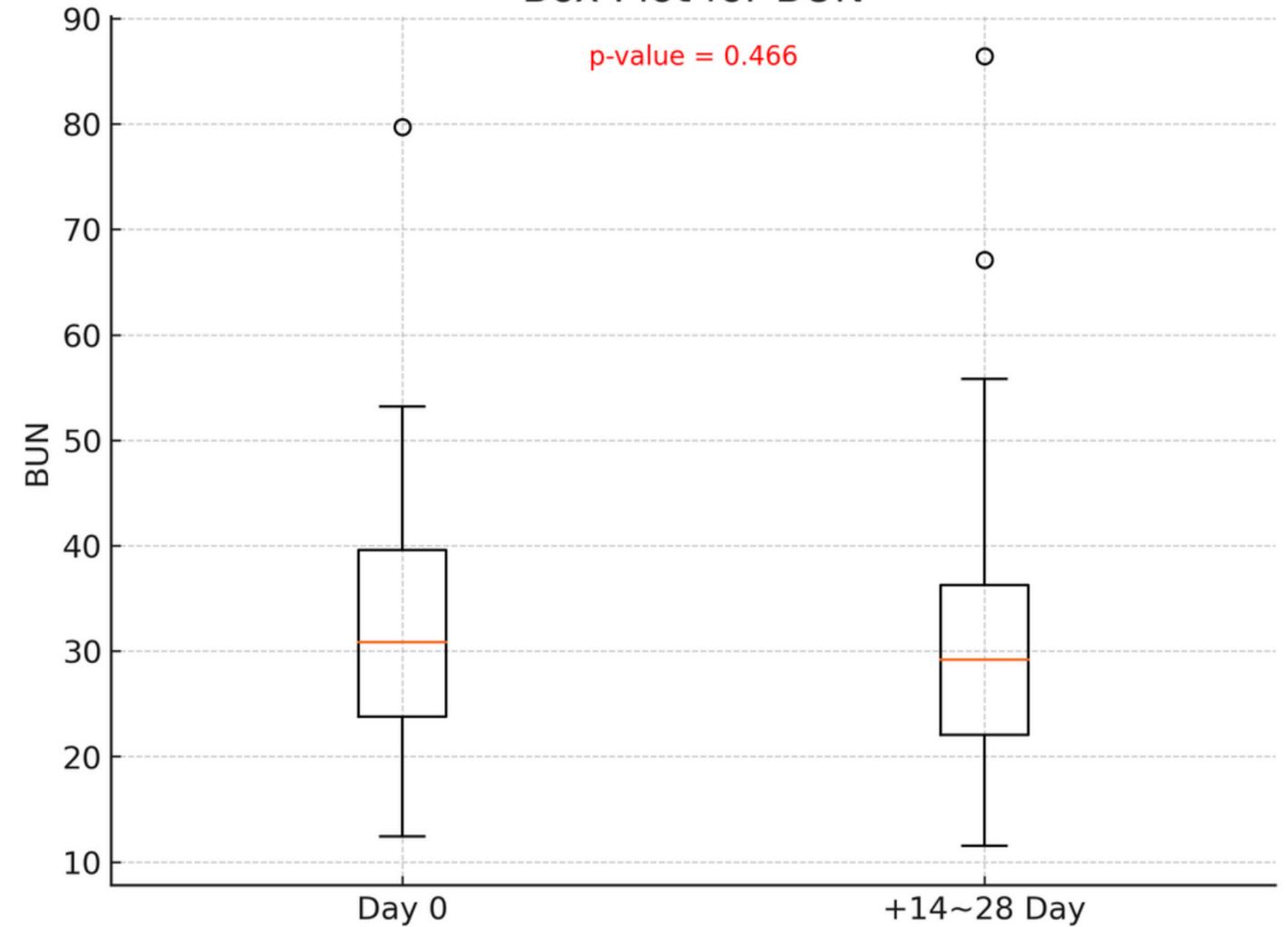
Box Plot for Crea

p-value = 0.607



Box Plot for BUN

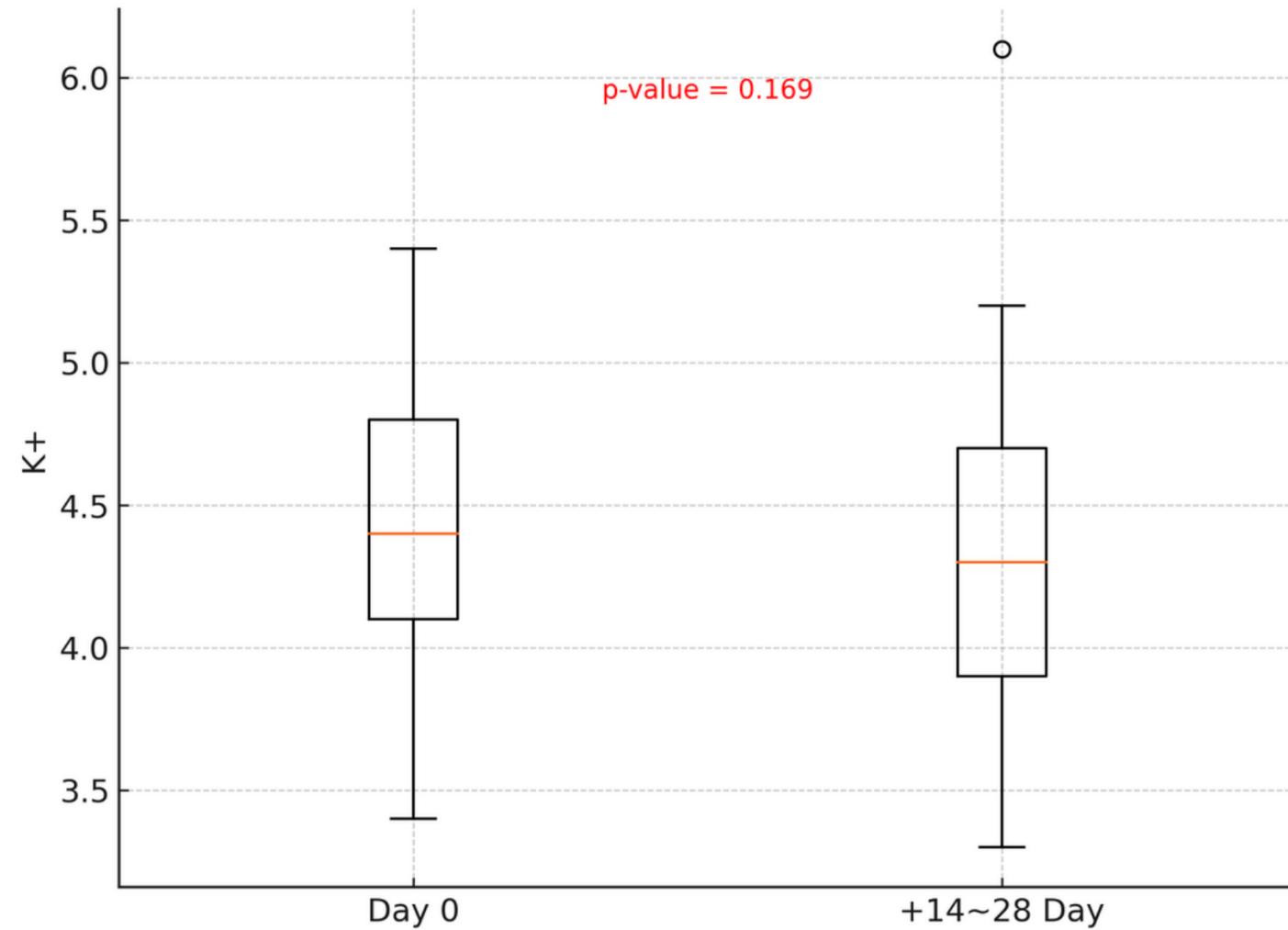
p-value = 0.466



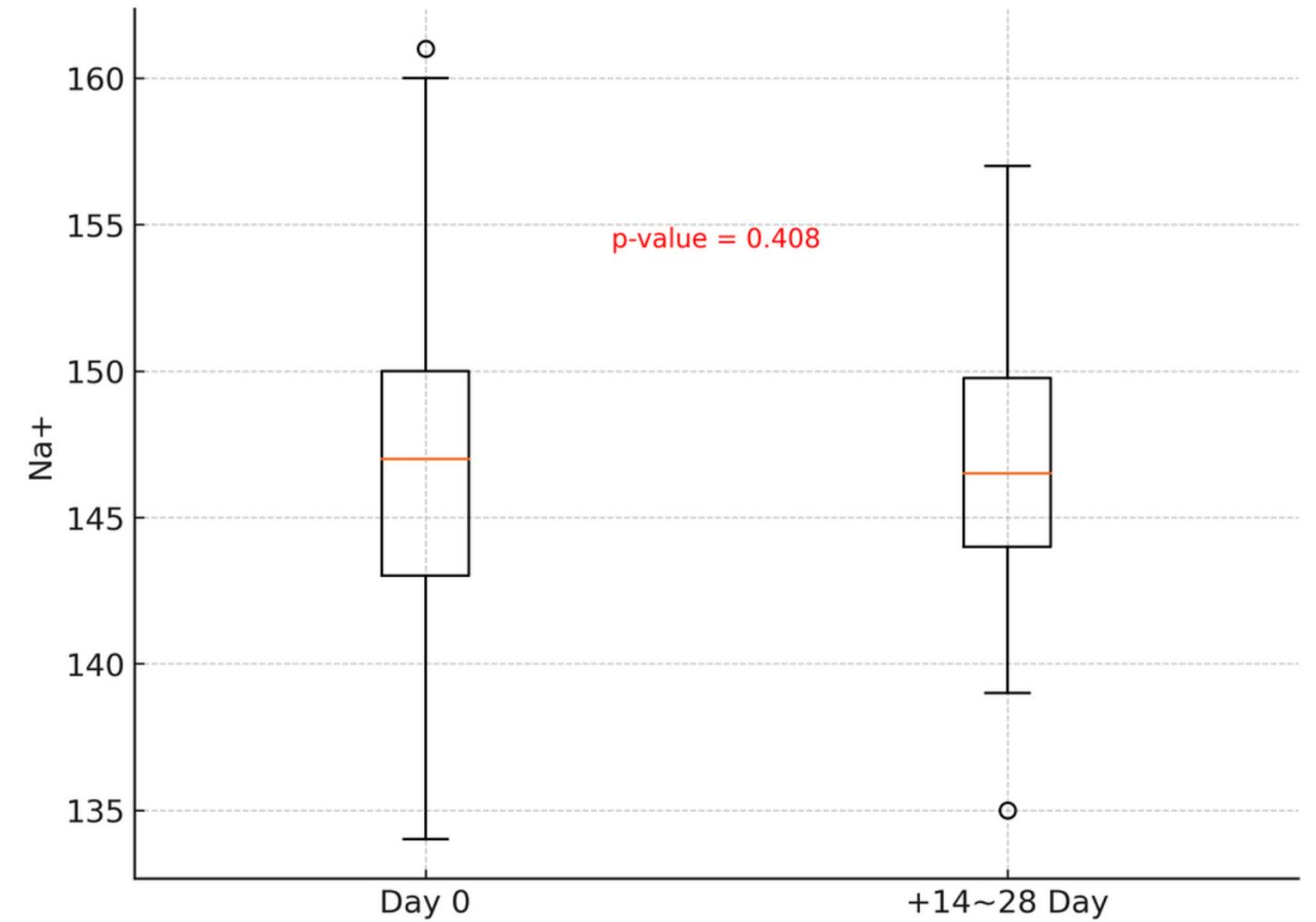
# 결과 - B2 shortterm

Entresto -MMVD환자에 투약 후 회고적 고찰

Box Plot for K+

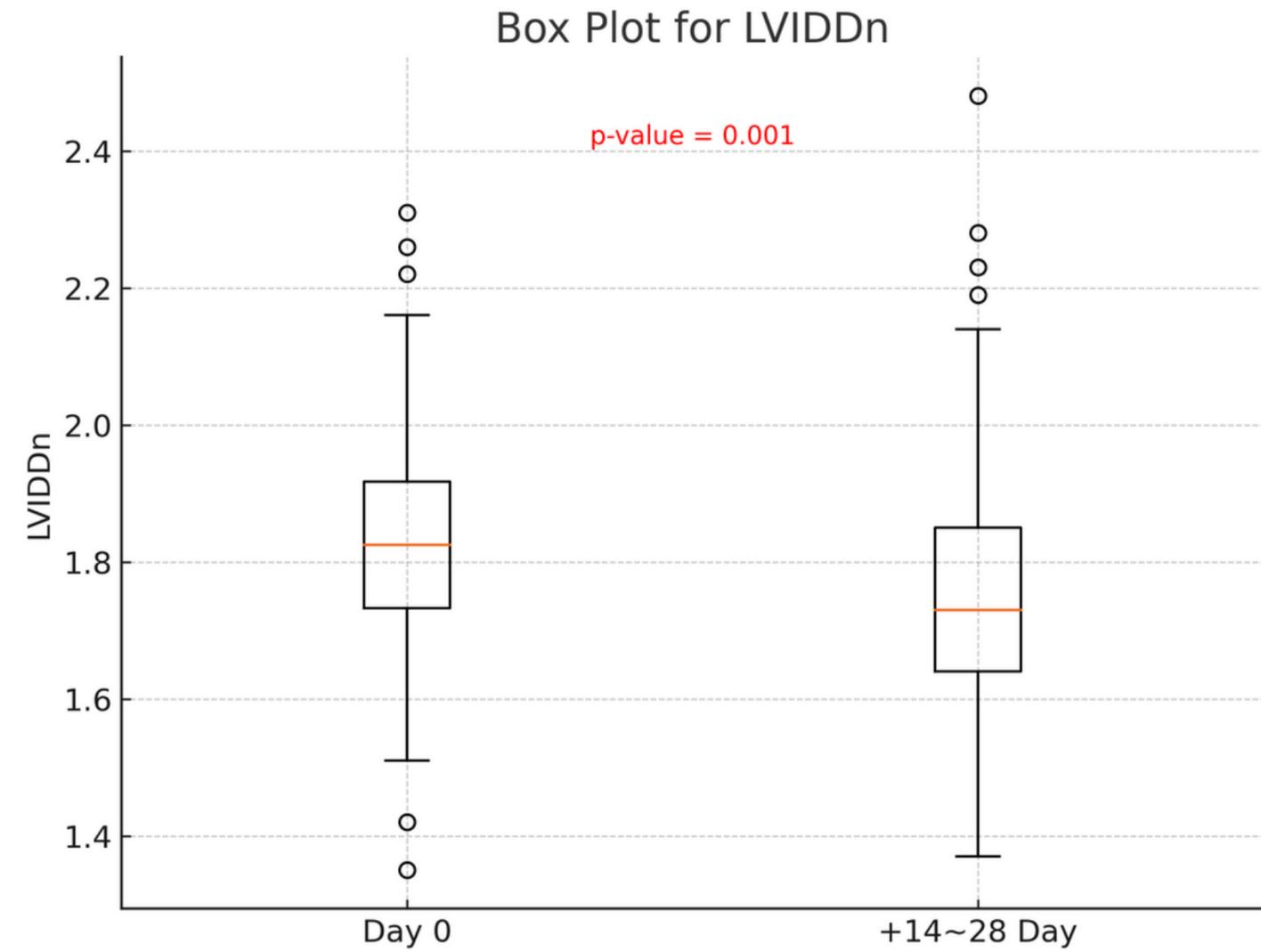
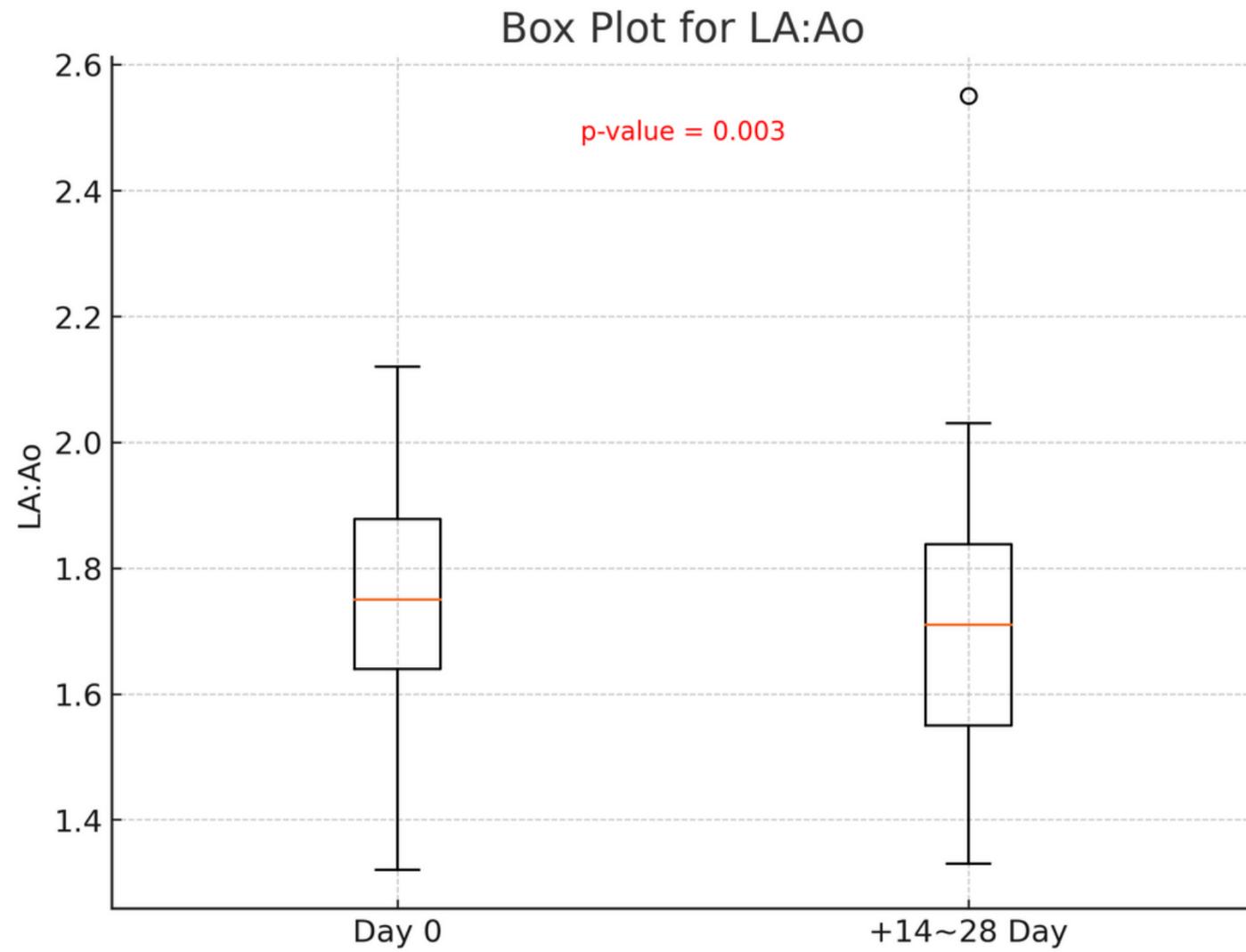


Box Plot for Na+



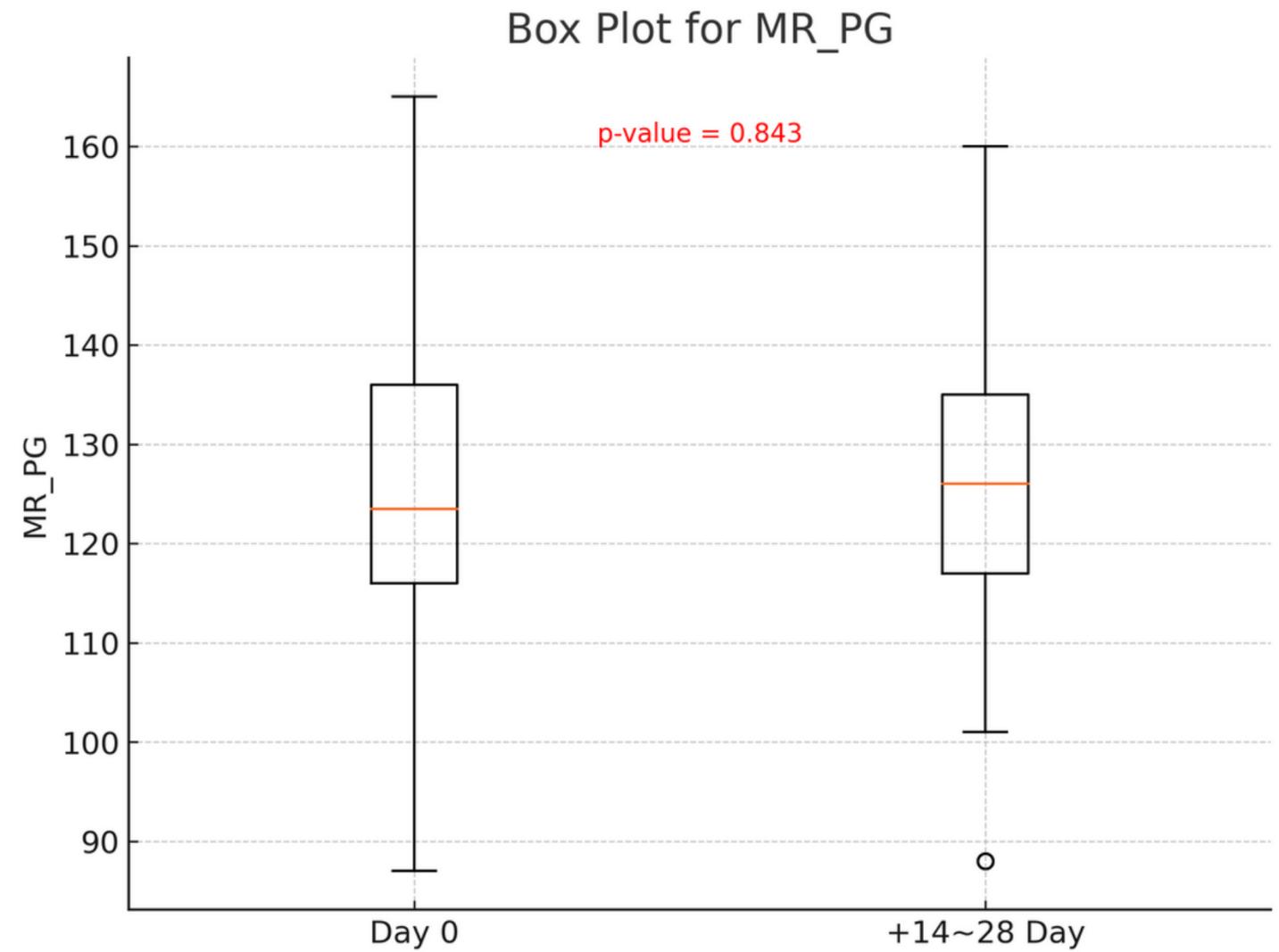
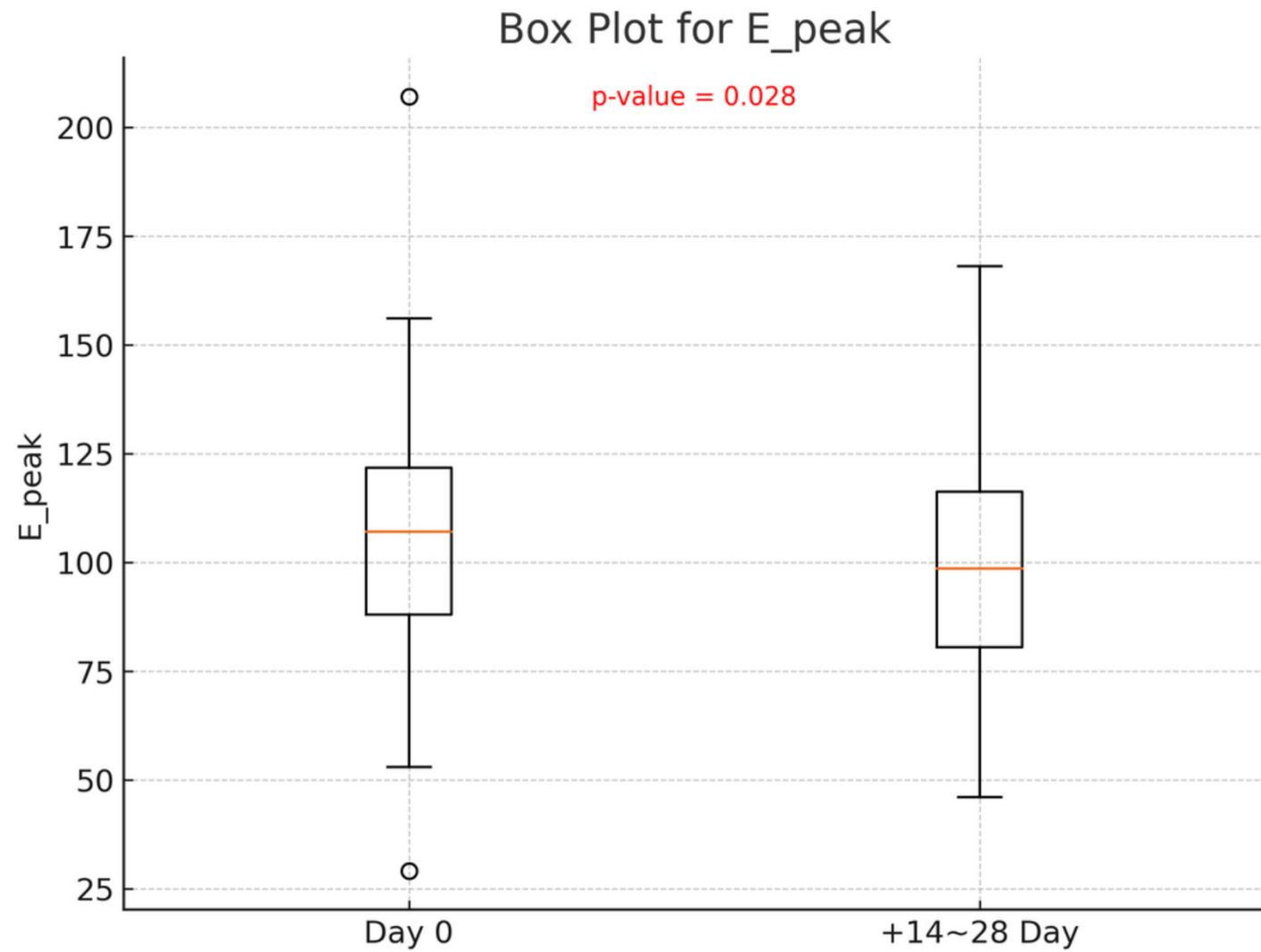
# 결과 - B2 shortterm

Entresto -MMVD환자에 투약 후 회고적 고찰



# 결과 - B2 shortterm

Entresto -MMVD환자에 투약 후 회고적 고찰



# 결과 - B2 Longterm

Entresto -MMVD환자에 투약 후 회고적 고찰

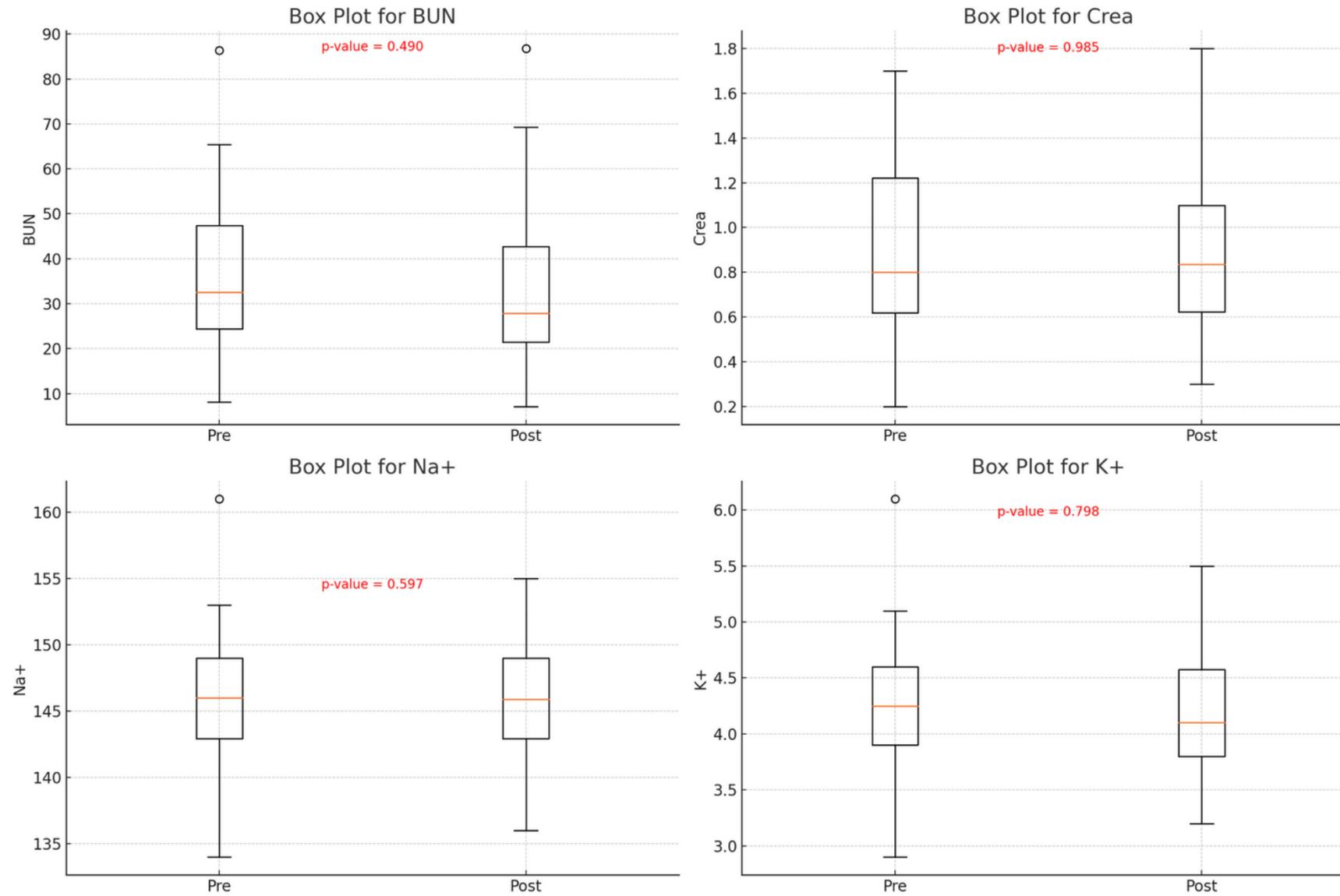
*N=50*

Variables	Day 0 (Mean ± SD)	Day 180~360 (Mean ± SD)	P-value
BUN	35.44 ± 16.99	32.96 ± 17.50	0.49
Crea	0.89 ± 0.39	0.89 ± 0.36	0.99
Na+	145.95 ± 4.76	145.48 ± 4.82	0.60
K+	4.25 ± 0.57	4.22 ± 0.53	0.80

Bun(mg/dL),Crea(mg/dL), Na(mmol/L), K(mmol/L)

# 결과 - B2 Longterm

Entresto -MMVD환자에 투약 후 회고적 고찰



# 결과 - C longterm

Entresto -MMVD환자에 투약 후 회고적 고찰

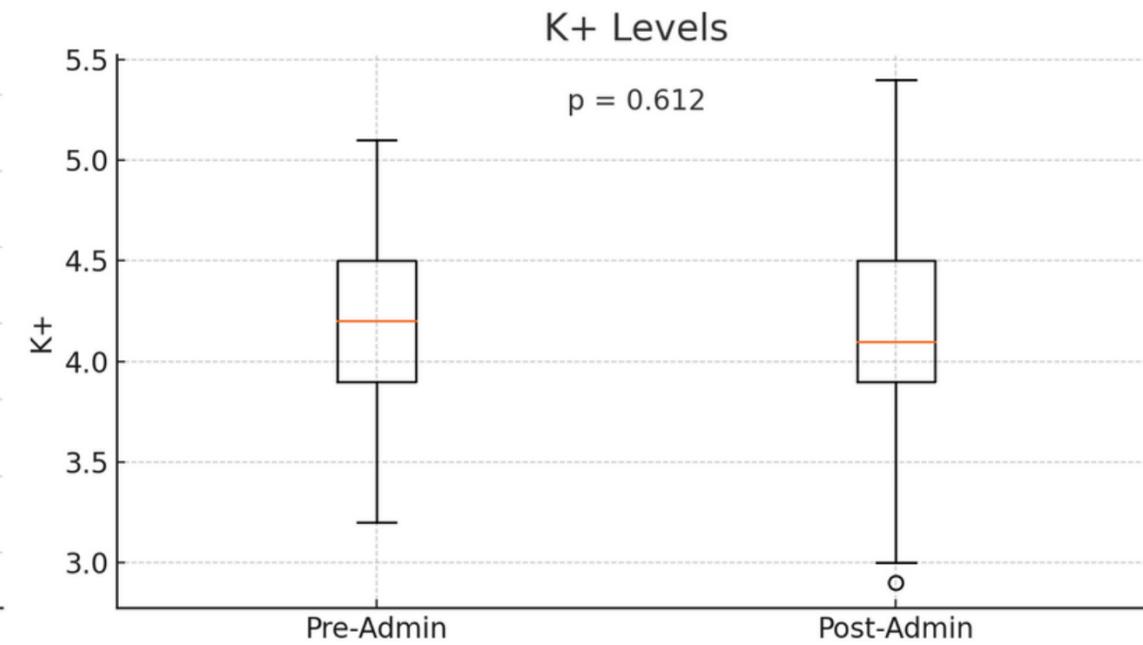
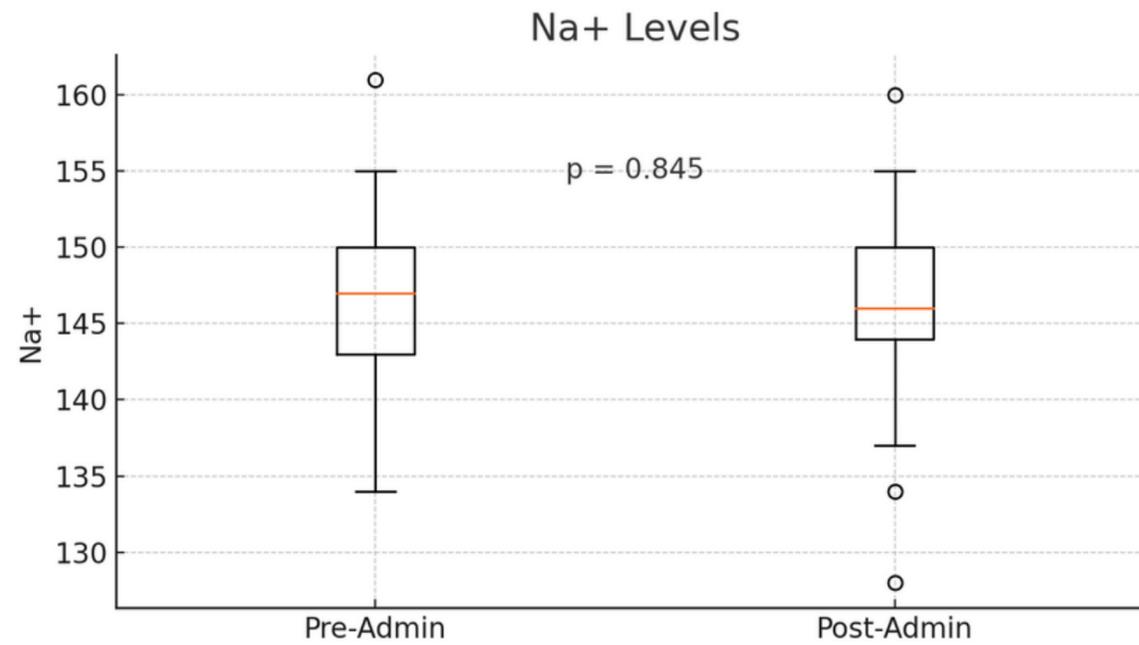
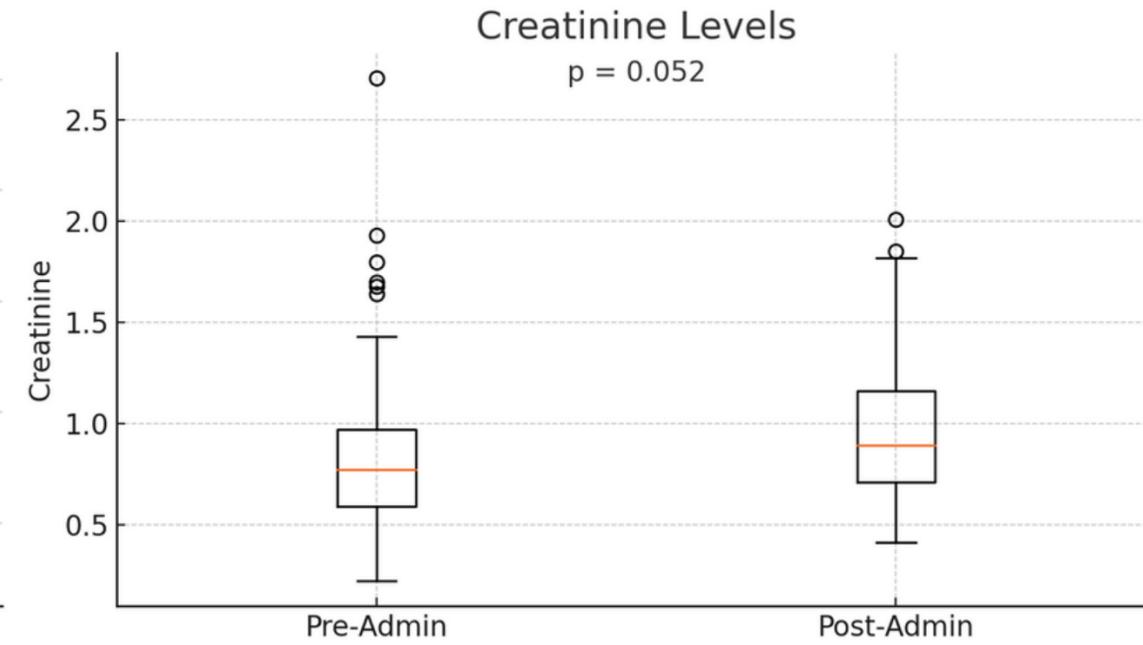
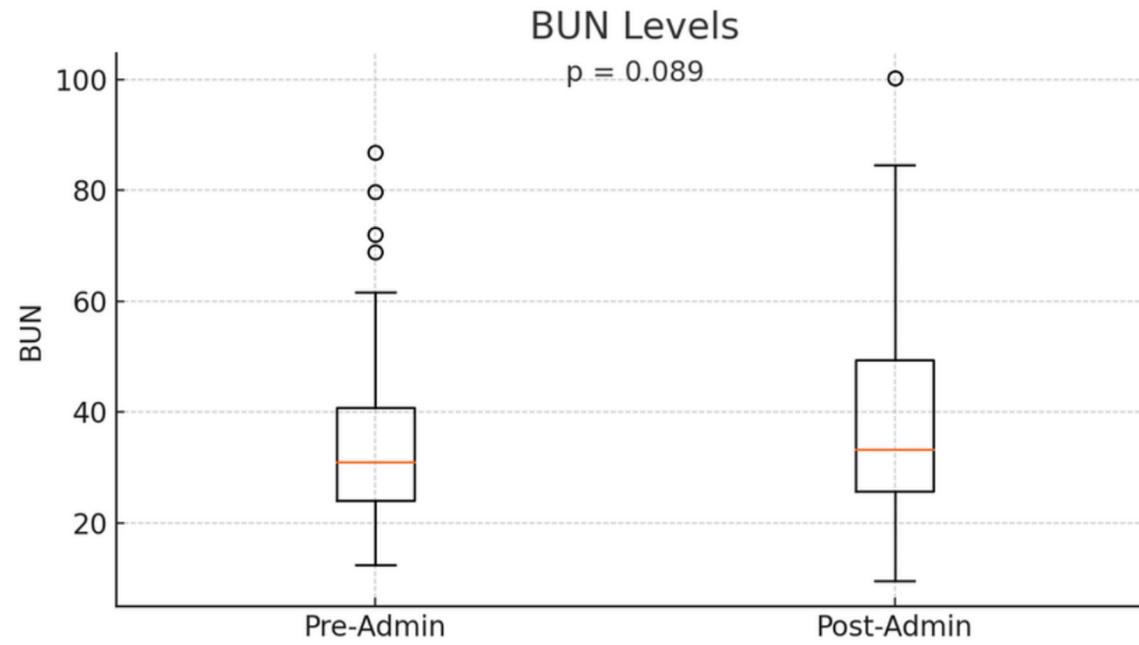
*N=64*

Variables	Day 0 (Mean $\pm$ SD)	Day 180+ (Mean $\pm$ SD)	P-value
BUN	35.46 $\pm$ 16.54	40.40 $\pm$ 21.07	0.09
Crea	0.87 $\pm$ 0.48	0.97 $\pm$ 0.38	0.05
Na+	146.57 $\pm$ 4.94	146.39 $\pm$ 5.33	0.85
K+	4.21 $\pm$ 0.45	4.17 $\pm$ 0.52	0.61

Bun(mg/dL),Crea(mg/dL), Na(mmol/L), K(mmol/L)

# 결과 - C longterm

Entresto -MMVD환자에 투약 후 회고적 고찰



## 데이터들의 한계점

1. 술자 평가 한계 - 주관 개입?
2. 기저질환, 먹는약등 통제되지 않은 통계군
3. Prospective, randomized, double-blind placebo-controlled study의 필요성

# 임상 적용의 한계점

1. 약물의 오남용에 대한 우려?
2. 약물 투여의 기준?
3. 비용 vs 효과

# 결론

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# 결론

RAAS의 과항진은 이첨판 폐쇄부전을 악화시키는 요인으로 알려져 있습니다.

인간의 새로운 RAAS 차단제 Entresto(ARNi)는 심부전에서 기존의 RAAS 차단제에 비해 월등한 것으로 결론이 났습니다.

MMVD 환자에서 Entresto 투여 후 Long, Short term 에서 유의미한 부작용이 관찰되지 않았습니다.

동시에 상대적으로 뚜렷한 좌심방압, 좌심방 크기 감소가 관찰되었습니다.

회고적 통계의 한계점에도 불구하고, 상대적으로 많은 환자가 평가되어 약물의 위험성은 낮은 것으로 고려됩니다.

기존의 RAAS 차단제의 효과가 불충분하다고 판단 될 경우, 투여를 고려해볼 수 있습니다.

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Q&A

질의 응답

