The Decrement of Hemoglobin Concentration with Angiotensin II Receptor Blocker Treatment is Correlated with the Reduction of Albuminuria in Non-Diabetic Hypertensive Patients: Post-hoc Analysis of ESPECIAL Trial

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ABSTRACT

Blockade of the renin-angiotensin-aldosterone system exhibits a renoprotective effect; however, blockade of this system may also decrease hemoglobin (Hb) and erythropoietin (EPO) levels. We evaluated the correlation between reduced albuminuria and decreased hemoglobin concentrations after treatment with an angiotensin II receptor blocker (ARB). Two hundred forty-five non-diabetic hypertensive participants with established albuminuria and relatively preserved renal function were treated with an ARB (40 mg/day olmesartan) for eight weeks. Subsequent changes in various clinical parameters, including Hb, EPO, and albuminuria, were analyzed following treatment. After the 8-week treatment with an ARB, Hb and EPO levels significantly decreased. Patients with a greater decrease in Hb exhibited a greater reduction in 24-hour urinary albumin excretion compared with patients with less of a decrease or no decrease in Hb, whereas no associations with a decline in renal function and EPO levels were noted. Multivariate logistic regression analysis demonstrated a correlation between the reduction of urine albumin excretion and the decrease in Hb levels (after natural logarithm transformation, adjusted odds ratio 1.76, 95% confidence interval 1.21-2.56, P = 0.003). Linear regression analysis also supported this positive correlation (Pearson correlation analysis; R = 0.24, P < 0.001). Decreased Hb concentrations following ARB treatment were positively correlated with reduced albuminuria in non-diabetic hypertensive patients, regardless of decreased blood pressure and EPO levels or renal function decline.

BACKGROUND

- **Angiotensin II receptor blockers (ARBs)**
  - Lowering blood pressure (BP) and reducing proteinuria
  - Prevention of progressive renal dysfunction & cardiovascular morbidity and mortality
  - Pivotal treatments for diabetic and non-diabetic patients with chronic kidney disease

N Engl J Med 2000; 342: 145-153
Diabetes Care 2007; 30: 1577-1578
Int J Clin Pract 2005; 59: 1001-1004

- Adverse effect: decrement of hemoglobin (Hb) levels with a significant reduction in erythropoietin (EPO) levels

Transplantation 1995; 60: 132-137
Hypertens Res 2002; 25: 849-855
Am J Nephrol 2003; 23: 287-293

- However, most of these studies were conducted in relatively small study populations with diabetes mellitus or overt kidney disease, furthermore, the correlation between the reduction in albuminuria and the decrement in hemoglobin level has not been assessed thoroughly.

PURPOSE

- To determine **the lowering effects of an RAAS blockade** medication **(olmesartan) on Hb concentrations** and investigate the **main factors** related to decreased hemoglobin levels

- In particular, **the correlation or cause-effect relationship between reduced Hb concentrations and albuminuria** in non-diabetic hypertensive patients with albuminuria

METHODS

- **Post-hoc analysis of ESPECIAL trial**: Effects of Intensive Low-Salt Diet Education on Albuminuria among Nondiabetic Patients with Hypertension Treated with Olmesartan: A Single-Blinded Randomized, Controlled Trial (clinicaltrials.gov registration number NCT01552954)

Clin J Am Soc Nephrol 2014; 9: 2059-2069

- **Study populations**
  - 2012.3 ~ 2013.3, outpatient renal clinics of 7 centers in Korea
  - 245 non-diabetic hypertensive patients (> 19 years)
  - MDRD-eGFR ≥ 30 ml/min/1.73 m^2, random urine ACR ≥ 30 mg/g
  - Serum creatinine (sCr) levels measured ≥ 2 with an interval of 1 week or more in the last 6 months

- **Study protocol**
  - All patients were treated with **40 mg/day olmesartan medoxomil** during the overall study period
  - Week 8: randomization (intensive or conventional low salt diet education)

- **Week 0 and 8 data collection:** Hb, sCr, eGFR, EPO, 24-hour urine excretion of albumin, and creatinine clearance (CCr)

Conflict of interest: None declared

RESULTS

- **Baseline characteristics and laboratory findings according to study period**

	Baseline (0th week)	After 8 week	P
Age (years)	49.5 ± 13.3		
Male gender (n, %)	122 (49.8)		
Systolic BP (mmHg)	130.9 ± 11.8	122.6 ± 14.4	<0.001
Diastolic BP (mmHg)	79.4 ± 9.1	73.9 ± 10.3	<0.001
Blood measurements			
Hb (g/dL)	13.9 ± 1.7	13.6 ± 1.7	0.049
BUN (mg/dL)	17.2 ± 6.3	19.2 ± 7.8	0.005
sCr (mg/dL)	1.1 ± 0.4	1.2 ± 0.4	0.277
eGFR (mL/min/1.73m^2)	67.3 ± 24.6	64.7 ± 24.4	0.242
Uric acid (mg/dL)	6.4 ± 1.8	6.8 ± 1.8	0.009
Na^+ (mEq/L)	140.7 ± 2.2	140.5 ± 2.4	0.719
K^+ (mEq/L)	4.3 ± 0.4	4.5 ± 0.4	<0.001
EPO (U/L)	17.2 ± 12.1	14.9 ± 14.4	<0.001
Urine measurements			
24hr urine albumin (mg/day)	565.0 (242.7-1285.3)	281.0 (104.2-640.3)	<0.001
CCr (mL/min)	80.8 ± 34.1	77.0 ± 34.3	0.125

All data are expressed as mean ± standard deviation or median (interquartile range).

- **Laboratory findings at 8th week according to the decrement of hemoglobin level**

	Lesser decrease or increase (N = 126)	Greater decrease (N = 119)	P
Systolic BP (mmHg)	125.2 ± 14.6	119.7 ± 13.7	0.002
0th-8th Systolic BP (mmHg)	6.5 ± 16.1	10.3 ± 14.3	0.027
Hemoglobin (g/dL)	13.9 ± 1.7	13.2 ± 1.7	0.002
0th-8th Hb (g/dL)	-0.2 ± 0.4	0.9 ± 0.6	<0.001
eGFR (mL/min/1.73m^2)	64.6 ± 23.0	64.8 ± 26.0	0.897
0th-8th eGFR (mL/min/1.73m^2)	2.9 ± 8.0	2.3 ± 10.4	0.491
EPO (U/L)	15.2 ± 9.5	14.6 ± 18.2	0.010
0th-8th EPO (U/L)	2.7 ± 8.2	1.8 ± 18.5	0.831
24hr urine albumin (mg/day)	279.3 (104.2-737.0)	288.2 (101.0-597.0)	0.575
0th-8th 24hr urine albumin (mg/day)	126.1 (21.0-454.4)	317.5 (110.0-933.0)	<0.001
CCr (mL/min)	76.2 ± 34.1	77.8 ± 34.6	0.534
0th-8th CCr (mL/min)	5.3 ± 16.9	1.6 ± 20.1	0.091

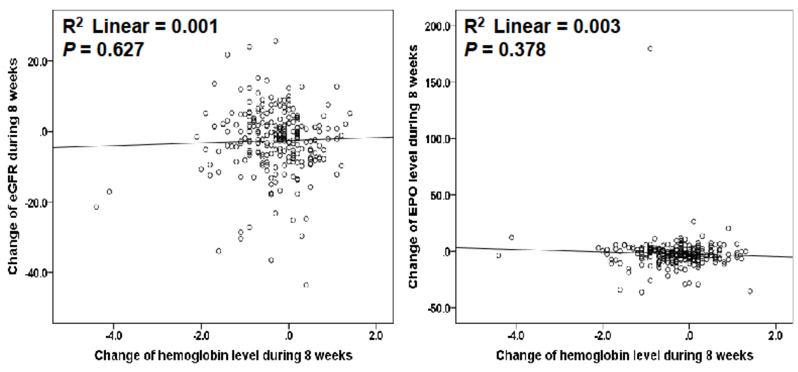
All data are expressed as mean ± standard deviation or median (interquartile range).

- **Baseline characteristics and laboratory findings according to the decrement of hemoglobin level**

	Lesser decrease or increase group (-1.4~0.2 g/dL) (N = 126)	Greater decrease group (0.3~4.4 g/dL) (N = 119)	P
Age (years)	50.2 ± 13.0	48.8 ± 13.7	0.351
Male gender (n, %)	64 (50.8)	58 (48.7)	0.748
Systolic BP (mmHg)	131.7 ± 11.3	130.0 ± 12.2	0.122
Diastolic BP (mmHg)	79.5 ± 9.0	79.4 ± 9.3	0.712
Blood measurements			
Hemoglobin (g/dL)	13.7 ± 1.6	14.1 ± 1.8	0.058
sCr (mg/dL)	1.1 ± 0.4	1.2 ± 0.5	0.902
eGFR (mL/min/1.73m^2)	67.4 ± 23.5	67.1 ± 25.9	0.890
Na^+ (mEq/L)	140.7 ± 2.2	140.7 ± 2.2	0.989
K^+ (mEq/L)	4.3 ± 0.4	4.3 ± 0.4	0.084
EPO (U/L)	17.9 ± 13.4	16.4 ± 10.6	0.222
Urine measurements			
24hr urine albumin (mg/day)	488.2 (210.0-1171.0)	715.2 (330.6-1366.0)	0.101
CCr (mL/min)	81.9 ± 32.5	79.6 ± 35.9	0.447

All data are expressed as mean ± standard deviation or median (interquartile range).

- **Correlation between the decrease in Hb level and the decline in eGFR (Lt.) or in EPO levels (Rt.)**



- **Comparison according to the reduction in albuminuria for 8 weeks**

	Lesser reduction group (< 50%) (N = 129)			Greater reduction group (≥ 50%) (N = 114)			P^b	P^c	P^d
	0th week	8th week	0th – 8th	0th week	8th week	0th – 8th			
Age	51.7 ± 12.1			46.9 ± 14.4			0.005		
Systolic BP (mmHg)	131.3 ± 12.3	126.5 ± 14.0	4.8 ± 14.9	130.5 ± 11.3	118.3 ± 13.6	12.2 ± 15.0	0.845	<0.001	<0.001
Diastolic BP (mmHg)	80.3 ± 9.3	76.2 ± 10.7	4.1 ± 11.1	78.5 ± 8.8	71.5 ± 9.2	7.0 ± 10.3	0.069	<0.001	0.128
Hemoglobin (g/dL)	14.0 ± 1.8	13.8 ± 1.7	0.1 ± 0.7	13.8 ± 1.7	13.3 ± 1.7	0.5 ± 0.8	0.517	0.018	<0.001
eGFR (mL/min/1.73m2)	68.1 ± 25.3	67.1 ± 25.5	1.0 ± 8.3	66.3 ± 23.8	61.9 ± 22.7	4.4 ± 9.9	0.602	0.133	0.002
EPO (U/L)	17.1 ± 13.3	15.2 ± 10.6	1.9 ± 7.5	17.2 ± 10.8	14.7 ± 17.8	2.5 ± 19.1	0.648	0.173	0.059
24hr urine Na^+ (mEq/day)	154.1 ± 68.4	172.2 ± 77.0	-18.1 ± 66.5	155.4 ± 71.8	139.0 ± 64.0	16.4 ± 66.4	0.828	0.001	<0.001
24hr urine albumin (mg/day)	523.0 (158.0-1149.5)	490.0 (166.9-896.7)	62.8 (-16.8-234.0)	675.0 (316-1508)	197.2 (80.0-389.0)	454.2 (214-1041)	0.039	<0.001	<0.001
Cr clearance (mL/min)	80.8 ± 36.8	79.3 ± 34.8	0.9 ± 17.6	81.1 ± 31.1	74.4 ± 33.6	6.3 ± 19.2	0.701	0.275	0.001

[a] All data are expressed as mean ± standard deviation or median (interquartile range).
[b] P-value for comparison between lesser- and greater- reduction group at baseline
[c] P-value for comparison between lesser- and greater- reduction group after 8 weeks
[d] P-value for comparison of the changes during 8 weeks between lesser- and greater- reduction group

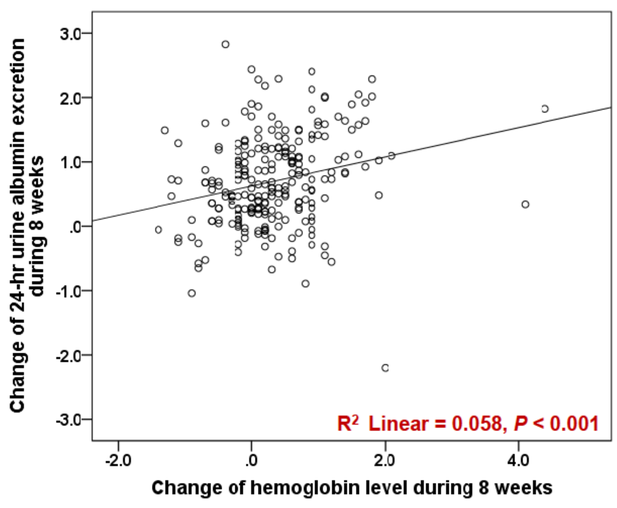
- **Multivariate logistic analysis for the decrement of Hb level**

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age (10-yr increment)	0.92 (0.77-1.12)	0.413	0.97 (0.80-1.18)	0.785
Male gender	0.92 (0.56-1.52)	0.748	0.90 (0.54-1.51)	0.699
0th-8th eGFR (per 10 mL/min/1.73m2)	0.94 (0.72-1.24)	0.664	0.85 (0.64-1.14)	0.280
0th-8th Systolic BP (per 10 mmHg)	1.17 (0.99-1.39)	0.059	1.10 (0.92-1.31)	0.283
0th-8th Ln (24-h urine albumin)	1.71 (1.18-2.48)	0.004	1.76 (1.21-2.56)	0.003

0th-8th Ln (24-h urine albumin)	Multivariate logistic analysis		
	Model 1*	Model 2†	Model 3‡
OR (95% CI)	1.71 (1.18-2.48)	1.71 (1.18-2.48)	1.76 (1.21-2.56)
***P*-value**	0.004	0.004	0.003

*Unadjusted model
†Model 1 + adjustment for age, gender, and the difference in eGFR during 8 weeks
‡Model 2 + adjustment for the difference in systolic blood pressure during 8 weeks

- **Correlation between the reduction in 24-hr urine albumin excretion and Hb levels**



CONCLUSION

- The administration of **angiotensin II receptor blocker therapy for 8 weeks** significantly decreased Hb and EPO levels. **The greater decrease in Hb levels** was closely correlated with a **greater reduction in albuminuria**, **regardless of the decrease of BP or the decline in renal function or EPO levels**.
- Our findings suggest **prominent preventative mechanisms for the progression of CKD** caused by ARBs and the crucial clinical implications of **ARB treatment in non-diabetic hypertensive patients**.

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