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RenalGuard System for the prevention of acute kidney injury in patients undergoing transcatheter aortic valve implantation

Gabriella Visconti[1], MD; Amelia Focaccio[1], MD; Michael Donahue[1], MD; Bruno Golia[1], MD; Antonio Marzano[1], MD; Elvira Donnarumma[2], PhD; Bruno Ricciardelli[1], MD; Lucio Selvetella[3], MD; Luigi Marino[4], MD; Carlo Briguori[1]*, MD, PhD

1. Laboratory of Interventional Cardiology and Department of Cardiology, Clinica Mediterranea, Naples, Italy; 2. IRCCS SDN, Naples, Italy; 3. Department of Vascular Surgery, Clinica Mediterranea, Naples, Italy; 4. Department of Cardiac Surgery, Clinica Mediterranea, Naples, Italy

KEYWORDS

- aortic valve stenosis
- complication
- kidney
- prevention

Abstract

Aims: We aimed to assess whether the RenalGuard™ System is effective in preventing acute kidney injury (AKI) following transcatheter aortic valve implantation (TAVI).

Methods and results: Forty-eight consecutive patients with chronic kidney disease (CKD) scheduled for TAVI were assigned to: 1) hydration with sodium bicarbonate solution (Control group), or 2) hydration with RenalGuard Therapy® (RenalGuard group). Hypotension was defined as periprocedural mean blood pressure <55 mmHg. The primary endpoint was the occurrence of AKI (i.e., an increase of ≥0.3 mg/dL in the serum creatinine concentration at seven days). AKI occurred in 10/26 (38.5%) patients in the Control group and in 1/22 (4.5%) patients in the RenalGuard group (p=0.005, odds ratio [OR] 0.076, 95% confidence interval [CI]: 0.009-0.66). RenalGuard Therapy protected against AKI (OR 0.71, 95% CI: 0.07-0.775, p=0.026), whereas post-procedural hypotension (OR 3.88, 95% CI: 1.06-14.24, p=0.040), and contrast media volume (OR 3.65, 95% CI: 1.15-5.75, p=0.043) increased the risk of AKI.

Conclusions: This non-randomised pilot study suggests that RenalGuard Therapy may be effective in preventing AKI in CKD patients undergoing TAVI.

**Corresponding author: Department of Interventional Cardiology, Clinica Mediterranea, Via Orazio, 2, I-80121 Naples, Italy. E-mail: carlobriguori@clinicamediterranea.it*

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Introduction

Acute kidney injury (AKI) is a common complication of transcatheter aortic valve implantation (TAVI)[1-3]. RenalGuard Therapy® (RenalGuard Solutions Inc., Milford, MA, USA) is effective in preventing contrast-induced AKI (CI-AKI)[4]. We herein report our experience with the RenalGuard System™ (RenalGuard Solutions Inc.) to prevent AKI in patients with chronic kidney disease (CKD) undergoing TAVI.

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Methods

This was a pilot, prospective, non-randomised study. From January 2009 to December 2014 all consecutive patients with CKD scheduled for TAVI through the femoral approach were included in the study. In all instances iodixanol was injected. Contrast media (CM) volume >3 times the estimated glomerular filtration rate (eGFR) was considered high[5]. The study was approved by our ethics committee and all patients signed written informed consent.

Patients were assigned to one of the following groups: 1) Control group, or 2) the RenalGuard group. Criteria for treating the patients with the RenalGuard System were: a) eGFR ≤30 mL/min/1.73 m^2, or b) a predicted risk for AKI ≥50%[6,7]. Patients allocated to the Control group received 154 mEq/L of sodium bicarbonate in dextrose and H_2O plus N-acetylcysteine (NAC) at a high dose[4]. In the RenalGuard group, hydration was carried out with normal saline using the RenalGuard System in order to achieve an optimal urine flow of ≥300 mL/hr[4].

The CoreValve ReValving™ prosthesis (Medtronic, Minneapolis, MN, USA) was implanted in all instances through the femoral approach. Hypotension was defined as mean blood pressure <55 mmHg at any time during or within the first 24 hours after the procedure, regardless of the need for vasopressor support[8]. The primary outcome measure was the development of AKI, defined as an increase in serum creatinine (sCr) concentration ≥0.3 mg/dL or ≥1.5-1.9 times above the baseline within seven days after the administration of contrast media[9]. Secondary endpoints and statistical analysis methods are reported in the **Appendix**.

Results

The characteristics of the patients in the two groups are reported in **Table 1**. Procedural details are reported in **Appendix Table 1**. The CM volume was similar in the two groups (RenalGuard group 188±59 mL; Control group 162±93 mL, p=0.25). Intraprocedural hypotension occurred in 17/26 (65.5%) in the Control group and in 13/22 (59%) in the RenalGuard group (p=0.76). Transfusion was required in six (23%) patients in the Control group and in five patients (23%) in the RenalGuard group (p=0.88). AKI occurred in 10/26 (38.5%) patients in the Control group and in 1/22 (4.5%) in the RenalGuard group (p=0.005; OR 0.076, 95% CI: 0.009-0.66) **(Figure 1)**. In-hospital renal failure requiring dialysis occurred in two patients in the Control group (8%) versus none in the RenalGuard group (p=0.49). RenalGuard Therapy protected against AKI, whereas post-procedural hypotension and contrast media volume increased the risk of AKI **(Table 2)**. Secondary endpoints are reported in the **Appendix**.

Table 1. Clinical characteristics of the patients included in the two groups.

	Control group (n=26)	RenalGuard group (n=22)	*p*-value
Age, years	82±5	85±3	0.044
Female	16 (62%)	18 (82%)	0.12
Body mass index, kg/m^2	27±3	27±4	0.64
Blood pressure, mmHg			
Systolic	134±14	132±25	0.30
Diastolic	78±7	73±7	0.11
Mean	97±8	91±10	0.07
AVA, cm^2	0.60±0.10	0.59±0.13	0.53
Aortic valve gradient, mmHg			
Peak	96±19	104±19	0.28
Mean	57±14	63±19	0.30
LV ejection fraction, %	53±9	54±6	0.80
Previous coronary bypass surgery	4 (15.5%)	2 (9%)	0.51
Previous PCI	6 (23%)	5 (23%)	0.98
Previous stroke	6 (23%)	1 (4.5%)	0.070
Systemic hypertension	25 (96%)	21 (95.5%)	0.90
Anaemia	10 (38.5%)	10 (45%)	0.43
Diabetes mellitus	11 (42%)	7 (32%)	0.22
Peripheral chronic artery disease	4 (15.5%)	2 (9%)	0.51
Log EuroSCORE I, median (range)	25 (13-37)	23 (10-32)	0.31
STS score – mortality, median (range)	6 (2-16)	10 (2-47)	0.035
Serum creatinine, mg/dL, median (IQR)	1.20 (1.00-1.77)	1.44 (1.15-2.29)	0.056
eGFR, ml/min/1.73 m^2	47±9	38±6	0.008
Serum cystatin C, median (IQR)	1.16 (1.00-1.60)	1.60 (1.25-2.09)	0.023
Hb, mg/dL	11.7±1.7	11.4±1.6	0.60
Contrast nephropathy risk score*			
Mehran et al	14±2	16±2	0.001
Gurm et al	8±4	16±4	0.003
STS score - renal failure, median (IQR)	9 (4-52)	13 (8-47)	0.033

*Contrast nephropathy risk score: the risk score proposed by Mehran et al includes both pre-procedural and procedural variables while that by Gurm et al includes only pre-procedural variables. AVA: aortic valve area; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; LV: left ventricular; PCI: percutaneous coronary intervention

Discussion

The present pilot study suggests that RenalGuard Therapy is effective in preventing AKI in patients with CKD undergoing TAVI. The

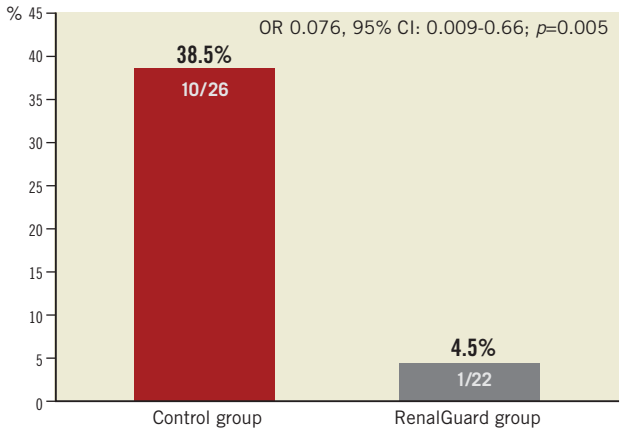


Figure 1. *Incidence of contrast-induced acute kidney injury.*

RenalGuard System enables the achievement of high urine output safely by maintaining the intravascular volume and minimising the risk of overhydration or underhydration[4]. The pathogenesis of AKI following TAVI encompasses "contrast-induced" and "contrast-independent" mechanisms. In the present study, post-procedural hypotension and CM volume represented independent predictors of AKI. A graded relationship between the length of time spent with a mean blood pressure (MAP) <55 mmHg and AKI has been reported[8]. As such, optimising perioperative haemodynamics may mitigate this complication. Although conflicting data have been reported[1], our result highlights the importance of limiting the CM volume in this high-risk population[2].

Study limitations

The limitations of the study are: 1) the small sample size, 2) the non-randomised design, and 3) the treatment of the Control group with sodium bicarbonate and NAC, which is actually not recommended[10]. A large randomised, multicentre trial comparing RenalGuard Therapy with the recommended hydration regimen (normal saline) is therefore necessary.

Conclusions

RenalGuard Therapy seems to be effective for AKI prevention in CKD patients undergoing TAVI.

Table 2. Protective and risk factors for acute kidney injury.

	Multivariable analysis			
	OR	95% CI	*p*-value	Bootstrap *p*-value*
RenalGuard Therapy	0.71	0.07-0.77	0.026	0.025
Hypotension	3.88	1.06-14.24	0.040	0.030
Contrast media volume >3x eGFR	3.77	1.13-4.51	0.041	0.029
Transfusion	3.55	0.74-16.14	0.101	0.074

*For the adjusted p-values, the bootstrap sampling method (100 reps) was employed. Hosmer-Lemeshow goodness-of-fit p=0.25.

Impact on daily practice

Acute kidney injury (AKI) is a frequent complication of transcatheter aortic valve implantation (TAVI) and may occur because of a combination of "contrast-induced" and "contrast-independent" (such as hypotension and transfusion) mechanisms. The RenalGuard Therapy has been reported to be an effective renoprotective strategy for contrast-induced AKI prevention. The present study supports the finding that the RenalGuard Therapy is more effective than a conventional hydration regimen in preventing AKI in patients with chronic kidney disease undergoing TAVI. Therefore, in daily practice we should include the RenalGuard System in our armamentarium for AKI prevention after TAVI.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Nuis RJ, Rodes-Cabau J, Sinning JM, van Garsse L, Kefer J, Bosmans J, Dager AE, van Mieghem N, Urena M, Nickenig G, Werner N, Maessen J, Astarci P, Perez S, Benitez LM, Dumont E, van Domburg RT, de Jaegere PP. Blood transfusion and the risk of acute kidney injury after transcatheter aortic valve implantation. *Circ Cardiovasc Interv.* 2012;5:680-8.

2. Yamamoto M, Hayashida K, Mouillet G, Chevalier B, Meguro K, Watanabe Y, Dubois-Rande JL, Morice MC, Lefevre T, Teiger E. Renal function-based contrast dosing predicts acute kidney injury following transcatheter aortic valve implantation. *JACC Cardiovasc Interv.* 2013;6:479-86.

3. Vahanian A, Alfieri O, Al-Attar N, Antunes M, Bax J, Cormier B, Cribier A, De Jaegere P, Fournial G, Kappetein AP, Kovac J, Ludgate S, Maisano F, Moat N, Mohr F, Nataf P, Pierard L, Pomar JL, Schofer J, Tornos P, Tuzcu M, van Hout B, Von Segesser LK, Walther T; European Association of Cardio-Thoracic Surgery; European Society of Cardiology; European Association of Percutaneous Cardiovascular Interventions. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2008;29:1463-70.

4. Briguori C, Visconti G, Focaccio A, Airoldi F, Valgimigli M, Sangiorgi GM, Golia B, Ricciardelli B, Condorelli G; REMEDIAL II Investigators. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. *Circulation.* 2011;124:1260-9.

5. Gurm HS, Dixon SR, Smith DE, Share D, Lalonde T, Greenbaum A, Moscucci M; BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) Registry. Renal function-based contrast dosing to define safe limits of radiographic contrast

media in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol.* 2011;58:907-14.

6. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol.* 2004;44:1393-9.

7. Gurm HS, Seth M, Kooiman J, Share D. A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol.* 2013;61:2242-8.

8. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology.* 2013;119:507-15.

9. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J.* 2012;33:2403-18.

10. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization. *EuroIntervention.* 2015;10:1024-94.

Supplementary data

Appendix. Methods and results details.

Appendix Figure 1. RenalGuard Therapy.

Appendix Figure 2. Serum creatinine kinetic.

Appendix Figure 3. Serum cystatin C kinetic.

Appendix Table 1. Procedural characteristics of the patients enrolled in the two groups.

Appendix Table 2. Distribution of the changes in serum creatinine and cystatin C levels in the two groups.

Supplementary data

Appendix. Methods and results details

METHODS

SECONDARY STUDY ENDPOINTS

1) An increase in sCr concentration ≥25% and ≥0.5 mg/dL.
2) The severity of AKI as follows: Stage 1, a sCr increase ≥0.3 mg/dL or ≥1.5-1.9 times from baseline; Stage 2, a sCr increase ≥2.0-2.9 times from baseline; and Stage 3, a sCr increase ≥3.0 times from baseline or the need for dialysis.
3) Changes in the serum cystatin C (sCyC) concentration at 24 and 48 hours after contrast media exposure.

STATISTICAL ANALYSIS

Continuous variables are given as mean±1 standard deviation or median and IQR, when appropriate. The Student's t-test and the non-parametric Mann-Whitney tests were used to determine differences between mean values for normally and abnormally distributed variables, respectively. Categorical variables were reported as percentages and were analysed by the Fisher's exact test, as appropriate. Linear regression was performed to provide odds ratios (OR) with 95% confidence intervals (CI) and adjustment for selected risk factors (treatment group, post-procedural hypotension, contrast media volume, and transfusion). To correct for multiple testing, 100 bootstrap iterations were computed. A probability level <0.05 was considered significant throughout the analysis. Data were analysed with SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

HYPOTENSION

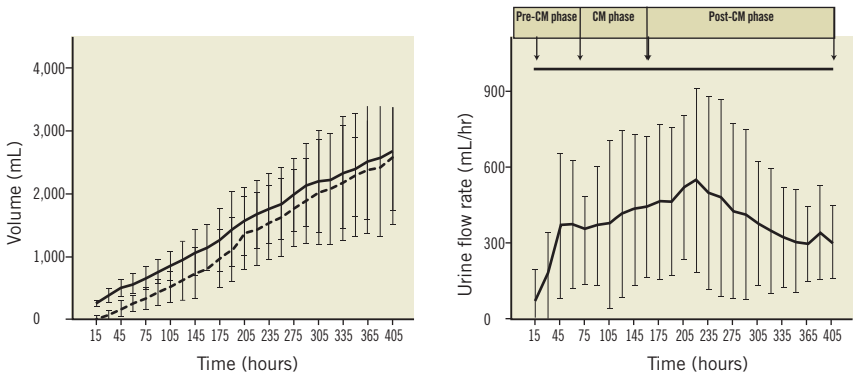
Duration of intraprocedural hypotension was 7.5 (3.5-19) minutes in the Control group and 6 (5-10) minutes in the RenalGuard group (p=1.00). Post-procedural hypotension occurred in 13/26 (50%) patients in the Control group and in 7/22 (32%) patients in the RenalGuard group (p=0.25). Duration of post-procedural hypotension was 90 (45-120) minutes in the Control group and 90 (44-145) minutes in the RenalGuard group (p=0.78).

HYDRATION VOLUME AND URINE VOLUME

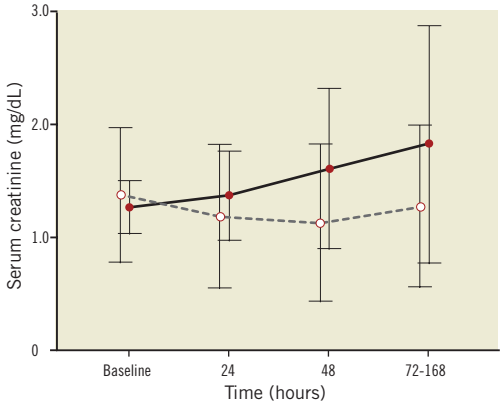
In the RenalGuard group, we observed highly accurate, temporally matched fluid replacement during the treatment **(Appendix Figure 1A)**, and the mean urine flow was 340±169 mL/hr **(Appendix Figure 1B)**. Total hydration volume was higher in the RenalGuard group (2,728±938 mL versus 1,575±246 mL; p<0.001). Total urine volume was higher in the RenalGuard group at both 24 hours (2,709±1,296 mL versus 1,551±550 mL; p<0.001) and 48 hours (2,570±1,130 mL versus 1,634±922 mL; p=0.002). Periprocedural acute pulmonary oedema occurred in only one patient in the Control group.

AKI

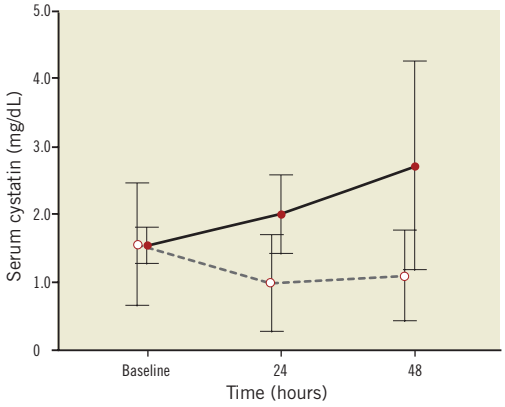
Serum creatinine increased significantly more in the Control group than in the RenalGuard group (p=0.014; F=4.73 by repeated measure of variance ANOVA model) **(Appendix Figure 2)**. In-hospital renal failure requiring dialysis occurred in two patients in the Control group (8%) versus none in the RenalGuard group (p=0.49). The distribution of different cut-offs of sCr increase at seven days, AKI severity and sCyC kinetic are reported in **Appendix Table 2** and **Appendix Figure 3**. The intraprocedural hypotension rate was similar in the AKI group and the No-AKI group (8/11 [70%] versus 20/35 [57%]; p=0.48). Post-procedural hypotension occurred in 9/11 (82%) patients in the AKI group versus 10/35 (31%) patients in the No-AKI group (OR 11.25, 95% CI: 2.06-61.50, p=0.002). The transfusion rate was higher in the AKI group than in the No-AKI group (6/11 [54.5%] versus 5/35 [14.5%], OR 7.2, 95% CI: 1.57-32.86, p=0.006).



Appendix Figure 1. *RenalGuard Therapy (mL/hr). A) Temporally matched fluid replacement during treatment by using the RenalGuard System (continuous line=infusion; dashed line=urine). B) Mean urine flow in the RenalGuard group. Urine output (mL/hr) was recorded every 15 minutes during RenalGuard Therapy. CM phase: contrast media exposure or intraprocedural time; Post-CM phase: post-contrast media or post-procedural time; Pre-CM phase: pre-contrast media exposure or pre-procedural time*



Appendix Figure 2. *Serum creatinine kinetic. Serum creatinine concentration (median and interquartile range) at baseline, 24 hrs, 48 hrs and peak within seven days after contrast media administration in the Control group (continuous line) and in the RenalGuard group (dashed line); p=0.014; F=4.73 by repeated measure of variance ANOVA model.*



Appendix Figure 3. *Serum cystatin C kinetic. Serum cystatin C concentration (median and interquartile range) at baseline, 24 and 48 hours after contrast media administration in the Control group (continuous line) and in the RenalGuard group (dashed line); p=0.006; F=6.68 by repeated measure of variance ANOVA model.*

Appendix Table 1. Procedural characteristics of the patients enrolled in the two groups.

	Control group (n=26)	RenalGuard group (n=22)	*p*-value
CoreValve size, mm			0.15
26	13 (50%)	9 (41%)	
29	13 (50%)	11 (50%)	
31	0	2 (9%)	
General anaesthesia,	1 (3.8%)	0	0.35
Elective	0	0	
Intraprocedural*	1 (3.8%)	0	
Second CoreValve deployment	2 (8%)	0	0.49
Definitive pacemaker	2 (8%)	5 (23%)	0.11
Peri-prosthesis leak	13 (50%)	11 (50%)	1.00
Trivial	12 (46%)	10 (45.5%)	
Mild	1 (4%)	1 (4.5%)	
Severe	0	0	
Transfusion	6 (23%)	5 (23%)	0.88
Volume of contrast media (mL)	188±59	162±93	0.25
Contrast volume >3x eGFR#	20 (77%)	16 (73%)	0.74
Procedural duration (minutes)	75±27	67±29	0.33
Femoral access technique			0.66
Percutaneous	23 (88.5%)	20 (91%)	
Surgical*	3 (11.5%)	2 (9%)	

*Including one patient who required surgical suture because of failure of closure device. #according to Gurm et al[5].

Appendix Table 2. Distribution of the changes in serum creatinine and cystatin C levels in the two groups.

	Control group (n=26)	RenalGuard group (n=22)	*p*-value
Changes in creatinine within 7 days			
Increase ≥0.3 mg/dL	10 (38.5%)	1 (4.5%)	0.005
Increase ≥0.5 mg/dL	7 (27%)	1 (4.5%)	0.038
Increase ≥25%	10 (38.5%)	1 (4.5%)	0.005
Increase ≥50%	6 (23%)	1 (4.5%)	0.070
Changes in creatinine according to VARC-2 criteria			
Stage 1	6 (23%)	1 (4.5%)	0.070
Stage 2	2 (8%)	0	0.49
Stage 3	2 (8%)	0	0.49
Changes in cystatin C at 24 hours			
Increase ≥0.3 mg/dL	11 (42%)	2 (9%)	0.020
Increase ≥10%	13 (50%)	3 (11.5%)	0.004