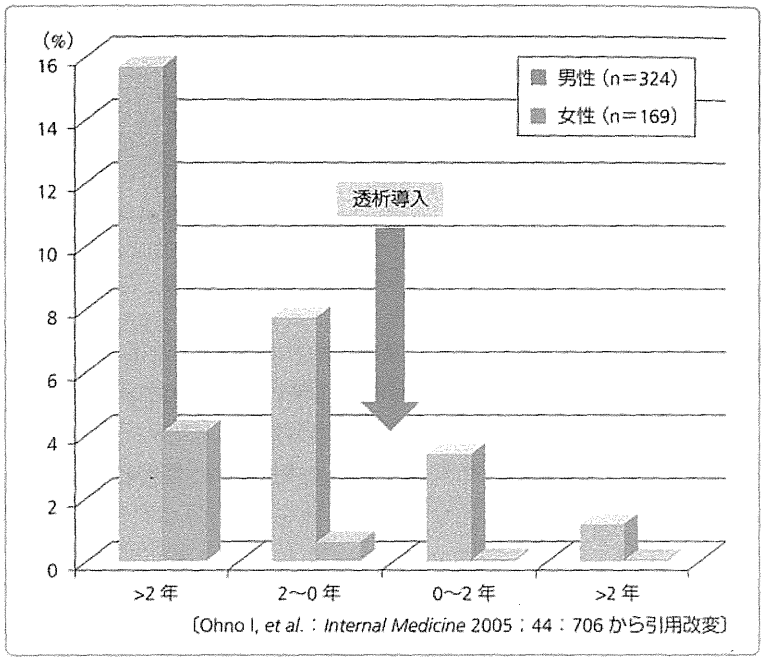
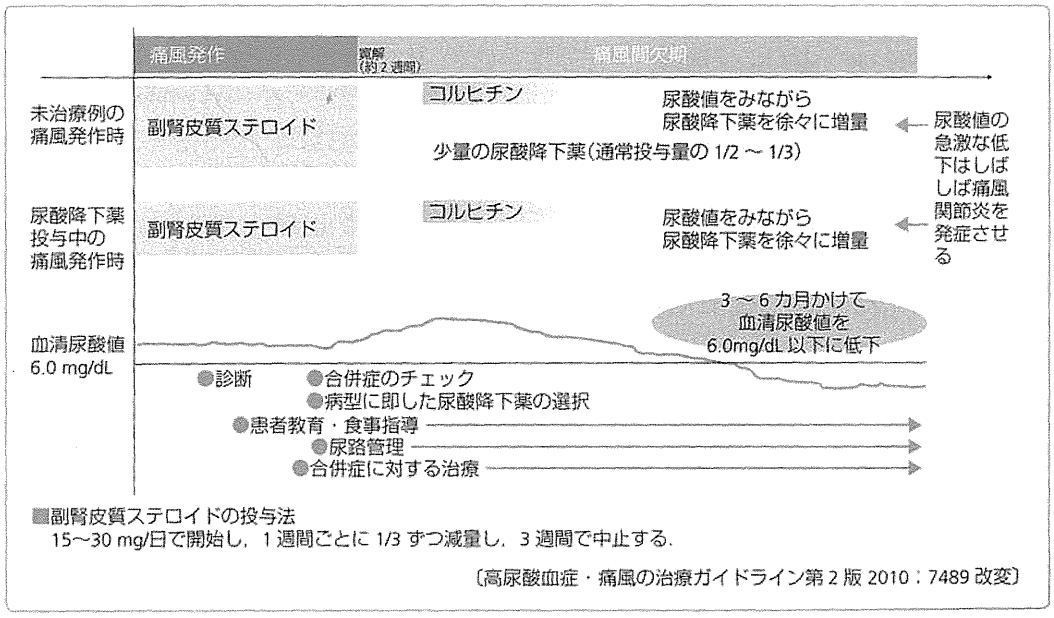


〔Ohno I, *et al.*：*Internal Medicine* 2005；44：706 から引用改変〕

図 1 末期腎不全患者の痛風発作頻度



〔高尿酸血症・痛風の治療ガイドライン第 2 版 2010：7489 改変〕

図 2 CKD 患者での痛風発作（痛風関節炎）時の治療

1 錠（0.5 mg）のみをタイミングよく服用できるよう，コルヒチンの携行を指導しておくことは有用である．なお，コルヒチンを痛風発作の極期に開始した場合，大量に用いても十分な有効性は得られず，副作用（腹痛，下痢，嘔吐，筋けいれんなど）の頻度が高いことが知られている．なお，コルヒチンは発作早期の治療のみならず，予防効果も期待できる．痛風発作が頻発する際や，尿酸降下薬の投与開始時に急速な血清尿酸値の低下に伴う痛風発作が懸念

される場合などにはコルヒチン1日1錠連日服用させることがある(コルヒチン・カバー)．この場合には1～3か月継続し，中止とする．

腎機能低下時のコルヒチン使用については，添付文書上はクレアチニンクリアランス(Ccr)＞50 mL/分で，通常3～4 mg 分6～8，予防0.5～1 mg 分1，Ccr 10～50/mL/分およびCcr＜10mL/分まで慎重投与，血液透析(HD)患者では1回0.25 mg 週2回，慎重投与，となっている．すなわち，上記で解説したような，発作前兆期の1錠頓用にあたっては，腎機能による配慮はあまり必要がないものと考えられる．

発作期の治療

痛風発作時にはCKD非合併例では，NSAIDsを短期間のみ比較的多量用いることが原則である(NSAIDパルス療法)．ただし，痛風発作に保険適応を有する薬剤はあまり多いとはいえない(インドメタシン，ナプロキセン，オキサプロジン，プラノプロフェン)．具体例を示すと，ナプロキセン(ナイキサン®)の場合，300 mgを3時間ごとに3回，1日に限って投与する．その後も疼痛が残る場合には24時間の間隔をおいて，同じ投与法を繰り返す．それ以降の痛みに対しては，必要に応じてNSAIDsの常用量を使用することとされている．NSAIDパルスの副作用としては，胃潰瘍の誘発・増悪があるが，腎機能低下のリスクも高い．痛風発作をきたすような高尿酸血症患者では腎機能低下も合併する場合が多く，注意が必要である．

CKD症例で，上記のNSAIDパルスは，いうまでもなく腎機能への悪影響が懸念されるため実施しないことを勧める．代わって，副腎皮質ステロイド薬を経口にて用いる．プレドニゾロン15～30 mgを投与して関節炎を沈静化させ，1週ごとに1/3量を減量し，3週間で中止する方法がある．また，膝や肘関節に水腫を伴う関節炎を呈する場合には，無菌的穿刺にて関節液を排液し，その後に副腎皮質ステロイド薬を投与する．

その他の注意点

一般的な注意点としては，痛風発作時にはできるだけ患部を保護的に扱い，冷却する．また禁酒を原則とする．痛風発作時に血清尿酸値を変動させると，発作の増悪や遷延をきたしうるので，尿酸降下薬の開始は，発作中ではなく，痛風発作が沈静化した後とする．尿酸降下薬を服用中に痛風発作がみられた場合には，尿酸降下薬は同量で継続し，発作鎮静化の治療をあわせて行う．

痛風発作の予防には，血清尿酸値を6.0 mg/dL未満に維持することが重要である．これによって痛風結節も退縮することが示されている．

痛風発作時の治療の流れを図2に示す[2]．

文献

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(守山敏樹)

Hypertension Research (2012), 1–7

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ORIGINAL ARTICLE

Effects of valsartan on progression of kidney disease in Japanese hypertensive patients with advanced, predialysis, chronic kidney disease: Kanagawa Valsartan Trial (KVT)

Takashi Yasuda[1], Masayuki Endoh[2], Daisuke Suzuki[2], Asio Yoshimura[3], Terukuni Ideura[3], Kozo Tamura[4], Kouju Kamata[4], Yoshiyuki Toya[5], Satoshi Umemura[5] and Kenjiro Kimura[1], for the KVT Study Group

Suppression of the renin–angiotensin system is known to slow progression of chronic kidney disease (CKD). However, few trials have been performed with Japanese patients. This study investigated whether the angiotensin receptor blocker (ARB) valsartan would delay the progression of kidney disease more effectively than conventional treatment in Japanese hypertensive patients with advanced, predialysis CKD. In a multicenter, randomized, open-label trial, 303 patients with hypertension and CKD with serum creatinine levels $\geqslant 2.0\,mg\,dl^{-1}$ were assigned to receive either conventional therapy plus valsartan (valsartan add-on group) or conventional therapy without ARB (control group). The primary outcome was a change in serum creatinine levels. Changes in urinary protein levels and time to onset of renal events were analyzed as secondary end points. There were no between-group differences in blood pressure during the study. Changes in serum creatinine and urinary protein levels did not differ between the groups. However, the rate of renal events, including doubling of serum creatinine levels or end-stage renal disease, was significantly lower in the valsartan add-on group than in the control group. The addition of valsartan decreased the risk by 42.6% after adjustment for baseline variables. The addition of valsartan to conventional therapy significantly slowed the rate of renal function decline and delayed the need for renal replacement therapy in Japanese hypertensive patients with advanced CKD.
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Keywords: CKD; randomized controlled trial; valsartan

INTRODUCTION

The number of patients developing end-stage renal disease (ESRD) has increased continuously over the past 10 years in Japan.[1] Most of these patients have a progressive decline of renal function over many years before renal replacement therapy (RRT) is required. In numerous Western studies,[2,3] blockade of the renin–angiotensin system (RAS) with either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs) has been shown to delay the progression of disease in patients with chronic kidney disease (CKD). Based on these studies, many guidelines, including those from Japan, strongly recommend the use of ACEIs or ARBs in hypertensive patients with CKD. However, few trials have examined the effects of a RAS inhibitor on the progression of kidney disease in Japanese patients with hypertension and advanced, predialysis CKD. Given that Japanese and Western patients may have different responses to therapeutic agents, clinical data from other countries are not necessarily applicable to Japanese patients. Understanding the measures to prevent disease progression is an important goal for Japanese CKD patients. Among RAS inhibitors, ARBs are preferred in Japan because ACEIs cause a dry cough in a high proportion of the Asian population.[4] Therefore, the aim of the present study was to examine the add-on effects of one of the ARBs, valsartan, on the course of renal disease progression in Japanese patients with hypertension and advanced CKD.

METHODS

Study design

The Kanagawa Valsartan Trial (KVT) was a multicenter, prospective, randomized, open-label study of Japanese hypertensive patients with advanced CKD whose serum creatinine levels were $\geqslant 2.0\,mg\,dl^{-1}$. It was designed to evaluate

[1]Department of Medicine, Division of Nephrology and Hypertension, St Marianna University School of Medicine, Kawasaki, Japan; [2]Department of Internal Medicine, Division of Nephrology and Metabolism, Tokai University School of Medicine, Isehara, Japan; [3]Division of Nephrology, Showa University Fujigaoka Hospital, Yokohama, Japan; [4]Department of Nephrology in Internal Medicine, Kitasato University School of Medicine, Sagamihara, Japan and [5]Department of Medical Science and Cardiorenal Medicine, Graduate School of Medicine, Yokohama City University School of Medicine, Yokohama, Japan
Correspondence: Dr T Yasuda, Department of Medicine, Division of Nephrology and Hypertension, St Marianna University School of Medicine, 2-16-1 Sugao Miyamaeku Kawasaki, Kawasaki 216-8511, Japan.
E-mail: yasuda@marianna-u.ac.jp
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the effect of add-on valsartan on the rate of CKD progression and the incidence of cardiovascular disease. A total of 13 affiliated clinical sites in Kanagawa prefecture, Japan, contributed to this study. All attending physicians were qualified nephrologists.

The enrollment visit was followed by a 4-week run-in screening period during which all ARBs were discontinued and, if necessary, patients were switched to other antihypertensive drugs to control their hypertension. Blood pressure (BP) was measured twice, and urine and blood specimens were obtained for measurements of serum creatinine and urinary protein. Eligible patients were examined for up to 36 months after the start of the trial.

There are no epidemiological data concerning the prognosis of CKD patients with a serum creatinine level $\geqslant 2.0\,mg\,dl^{-1}$. However, our preliminary data suggested that the 3-year incidence of ESRD or a doubling of the serum creatinine level would be more than 50% in such patients. A 30% reduction in renal outcomes was assumed among those assigned to valsartan add-on treatment. On this basis, it was estimated that with a study sample of at least 339 patients (170 in each group), the study would have 80% power to detect a clinically important difference in renal outcome between the two groups over a 3-year follow-up period, with a two-sided, type 1 error rate of 5%. Accordingly, the target for enrollment was 400 patients.

The trial was overseen by independent executive, steering, and safety and event committees. The executive committee oversaw the study, including the design, and had full access to all of the data at the end of the study as well as the final responsibility for the decision to submit the manuscript for publication. The steering committee oversaw the conduct of the trial and was responsible for data management and statistical analysis, with confirmation by biostatisticians. The safety and event committee regularly monitored adverse events and relevant clinical events. All outcomes were also reviewed and adjudicated by the safety and event committee, whose members were unaware of the treatment assignments. The authors had complete control over the analysis and interpretation of the results, the writing of the manuscript and the decision to submit it for publication, and they vouched for the accuracy and completeness of the reported data, as well as the fidelity of the reported study to the protocol (KVT study organization and investigators have been posted on Hypertension Research's website as Supplementary Information).

The study protocol was registered in Clinical Trials.gov (NCT00190580). Good clinical practice guidelines in accordance with the Declaration of Helsinki were followed. The study was approved by the institutional review board at each site, and all patients provided written, informed consent.

Study participants

The trial involved male and female Japanese hypertensive patients aged $\geqslant 20$ years. Hypertension was defined as a BP $>130/85$ mm Hg on two consecutive measurements at the office during the screening period. Patients were eligible for enrollment if their serum creatinine concentration was $\geqslant 2.0\,mg\,dl^{-1}$ during the screening period.

The exclusion criteria were ESRD with RRT, polycystic kidney disease, collagen disease and malignant or accelerated hypertension.

Randomization and treatment assignments

During the 4-week screening phase, each patient's eligibility for the study was established. In patients who had used ARBs before the start of the study, ARBs were suspended during the 4-week screening phase. Eligible patients were randomly assigned to either conventional therapy with valsartan (the valsartan add-on group) or conventional therapy without ARBs (the control group). Conventional treatment consisted of lifestyle modification, diet therapy including salt and protein restriction, blood glucose control in patients with diabetes, lipid control in patients with dyslipidemia, control of anemia and serum potassium, calcium and phosphate levels and blood pressure control as indicated below. Nonpharmacologic and pharmacologic approaches to treatment of hypertension and CKD were recommended according to the guidelines.[5,6]

A concealed randomization scheme was generated by computer at the clinical trials center. Patients were divided into three groups according to their baseline serum creatinine level and urinary protein excretion, determined by the protein/creatinine ratio of a spot urine sample. The three groups of serum creatinine levels were classified as follows: group I, $\geqslant 2.0$ to $<3.0\,mg\,dl^{-1}$; group II, $\geqslant 3.0$ to $<4.0\,mg\,dl^{-1}$; and group III $\geqslant 4.0\,mg\,dl^{-1}$. The three groups were classified by urinary protein levels as follows: group I, $<1.0\,g\,gCr^{-1}$; group II, $\geqslant 1.0$ to $<3.5\,g\,gCr^{-1}$; and group III, $\geqslant 3.5\,g\,gCr^{-1}$. The randomization was stratified by centers, genders, serum creatinine groups and urinary protein groups to maintain balance between the two groups.

The initial target BP in both groups was $<130/85$ mm Hg according to the guidelines of the Japanese Hypertension Society 2000.[5] This was changed to $<130/80$ mm Hg based on the revised guidelines of the Japanese Hypertension Society 2004 after 1 January 2004.[6] To achieve the target BP, patients in the valsartan add-on group were initially given 40 mg of valsartan orally, once daily in the morning, and titrated up by 40 mg at 4- to 8-week intervals according to changes in the blood pressure, proteinuria, renal function and serum potassium level. A maximum of 160 mg per day of valsartan was permitted. If BP control was not achieved at this dosage, additional antihypertensive agents were added. In the control group, BP control was achieved by either an increase in the dose of their existing treatment or additional treatment other than an ARB, as needed. Antihypertensive agents including ACEIs were allowed in both groups to help patients achieve and maintain their target BP, although no ARB other than valsartan in the valsartan add-on group was permitted, and no ARB in the control group was permitted.

At enrollment, the patients' baseline characteristics, including sex, age, height, weight, symptoms and signs, risk factors for cardiovascular disease (smoking, dyslipidemia, diabetes mellitus and previous cardiovascular events) and diagnosis of primary disease of CKD with or without kidney biopsy were recorded. Patients were seen every 2–4 weeks, or at least every 3 months, for up to 3 years. At every visit, an attending physician took standard BP measurements with the patient at rest in a sitting position using a validated mercury sphygmomanometer. The timing of BP measurements was free in relation to the intake of medication. Blood and urine samples were obtained at a minimum of 3-month intervals during the trial. Clinical laboratory tests included urinalysis (protein, creatinine) and blood chemistry (creatinine, sodium, potassium, total cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol). The glomerular filtration rate was estimated using the equation of the Japanese Society of Nephrology[7] and categorized using the KDOQI (Kidney Disease Outcomes Quality Initiative) stages.[8]

End points

The primary end point was the course of renal function, that is, the change in serum creatinine levels during the study. The estimated glomerular filtration rate (eGFR) was also used to estimate the course of renal function. Participants who reached the two prespecified clinical end points, that is, ESRD with dialysis and renal transplantation needed or death, were treated as censored. Therefore, the course of renal function was also evaluated by the mean annual serum creatinine slope and the mean annual rate of decline in eGFR from baseline to the end of observation or the two specified end points.

Prespecified secondary end points included change in urinary protein levels; renal events, such as the doubling of serum creatinine levels, initiation of maintenance dialysis therapy or renal transplantation; cardiovascular events, such as the composite of cardiovascular complications including admission because of stroke, ischemic heart disease, heart failure and other vascular disease; and death from any cause. Any single doubling of the serum creatinine level required confirmation by one additional positive result from a separate serial test.

Statistical analysis

All analyses were performed according to the intention-to-treat principle. For the comparison of the control and valsartan add-on groups, the unpaired Student's *t*-test, Mann–Whitney *U*-test and the χ^2-test were used to compare findings, as appropriate. In the analysis of the differences among treatment groups in the overall changes of systolic and diastolic BP, serum creatinine, eGFR and proteinuria, a generalized linear mixed model was used. The cumulative event curves until the first occurring prespecified events were estimated with the Kaplan–Meier procedure and the log-rank test. Multivariate Cox regression analysis was used to estimate the hazard ratios and 95%

Table 1 Baseline clinical characteristics

	Control (n = 144)	*Valsartan (n = 149)*	P-*value*
Age, years	64.2 ± 12.2	64.1 ± 12.3	0.95
Male/female, *n* (%)	103/41 (71.5/28.5)	109/40 (73.2/26.8)	0.76
BMI (kg m^{-2})	23.6 ± 3.1	23.1 ± 3.3	0.22
Smoking, *n* (%)	28 (19.4)	30 (20.1)	0.88
Diabetes mellitus, *n* (%)	59 (41.0)	60 (40.3)	0.90
Dyslipidemia, *n* (%)	71 (49.3)	74 (49.7)	0.95
Ischemic heart disease, *n* (%)	21 (14.6)	18 (12.1)	0.53
Serum creatinine (mg dl^{-1})	3.20 ± 1.14	3.19 ± 1.14	0.96
2.0–3.0, *n* (%)	78 (54.2)	81 (54.4)	
3.0–4.0, *n* (%)	41 (28.5)	42 (28.2)	1.00
⩾4.0, *n* (%)	25 (17.4)	26 (17.4)	
eGFR (ml min^{-1} per 1.73 m^2)	17.2 ± 5.8	17.4 ± 6.1	0.73
SBP (mm Hg)	142.2 ± 18.1	143.6 ± 15.7	0.48
DBP (mm Hg)	77.9 ± 11.0	80.1 ± 10.7	0.08
Urinary protein (g day^{-1})	1.66 (0.70–3.16)	1.63 (0.70–3.47)	0.99
<1.0, *n* (%)	57 (39.6)	59 (39.6)	
1–3.5, *n* (%)	55 (38.2)	58 (38.9)	0.99
⩾3.5, *n* (%)	32 (22.2)	32 (21.5)	
Primary disease of CKD, n *(%)*			0.52
Diabetic nephropathy	48 (33.3)	49 (32.9)	
Hypertensive nephrosclerosis	25 (17.4)	30 (20.1)	
IgA nephropathy	15 (10.4)	12 (8.1)	
Other glomerulonephritis[a]	19 (13.2)	24 (17.4)	
Interstitial nephritis	2 (1.4)	3 (2.0)	
Other	1 (0.7)	4 (2.7)	
Unknown	34 (23.6)	25 (16.8)	

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
Data are expressed as means ± s.d. or number (percentage) of patients.
The *P*-values were calculated using Student's *t*-test for continuous variables and χ^2-test for categorical variables.
[a]Other glomerulonephritis includes primary, secondary and hereditary glomerulonephritis.

Table 2 Antihypertensive medications used in the screening period and final observation

	Control		*Valsartan*	
Antihypertensive agent	*Screening (%)*	*Final (%)*	*Screening (%)*	*Final (%)*
ARB	0.0	12.0	0.0	88.7
ACEI	43.1	50.0	38.9	25.5
Ca antagonist	80.6	83.1	79.2	78.0
β-Blocker	15.3	25.5	15.4	15.6
α-Blocker	15.3	35.9	18.1	16.3
Loop diuretics	28.5	46.8	26.8	53.9
Thiazide diuretics	3.5	5.6	3.4	5.0
Aldosterone antagonists	1.4	1.4	1.3	0.0
Others	0.0	4.2	0.0	2.7
Number	1.9 ± 1.0	2.7 ± 1.3	1.8 ± 1.1	3.0 ± 1.3

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; Ca, calcium.
Data are expressed as percentage or means ± s.d.

confidence intervals for the addition of valsartan compared with conventional treatment with adjustment for baseline covariates. All statistical analyses were performed using SPSS software for Windows, version 16 (SPSS Institute, Chicago, IL, USA). The values are expressed as the means ± s.d. for normally distributed data and the medians (interquartile range) for nonnormally distributed data unless otherwise indicated. Differences with $P<0.05$ were considered significant in all analyses.

RESULTS

Patient population

A total of 312 patients were enrolled between May 2003 and April 2007. During the 4-week run-in screening period, 9 patients were excluded for failure to follow-up (patients did not visit the clinic because they moved or for unknown reasons) or protocol violation, including 2 patients with polycystic kidney disease; thus, 303 patients underwent randomization. After randomization, 10 patients, 6 in the control group and 4 in the valsartan add-on group, could not be followed-up: 3 withdrew consent, 5 failed to follow-up and 2 patients moved. Therefore, 293 patients were included in the analysis. The last evaluation of patients without ESRD or death was performed during the 3 months before April 2008. Data were censored on 31 May 2008. The median follow-up period was 23.8 months (range: 0.9–36.0 months).

The baseline characteristics for each treatment group are shown in Table 1. The mean age of the patients was 64.1 ± 12.2 years, with 72% men. The mean serum creatinine level was 3.20 ± 1.14 mg dl^{-1}, and the mean eGFR was 17.3 ± 6.0 ml min^{-1} per 1.73 m^2. CKD was stage 3 in 2 patients, stage 4 in 174 patients and stage 5 in 117 patients. The mean BP was 142.9 ± 16.9/79.0 ± 10.9 mm Hg. The median urinary protein level was 1.65 (0.70–3.33) g gCr^{-1}, and 11.3% of patients had a urinary protein level <0.3 g gCr^{-1}. There were no significant differences in the baseline clinical characteristics between groups.

The main primary diseases were diabetic nephropathy (33.1%); hypertensive nephrosclerosis (18.8%); IgA nephropathy (9.2%); other glomerulonephritis including primary, secondary and hereditary glomerulonephritis (15.4%); interstitial nephritis (1.7%); others (1.7%); and unknown origin (20.1%). The occurrence of primary diseases did not differ significantly between groups. Of the 293 patients, 38 (13.0%) had been diagnosed by renal biopsy.

The types of medications taken by the participants are shown in Table 2. During the screening period, no patients took ARBs, 120 (41.0%) took ACEIs, 239 (79.9%) took calcium channel blockers and 52 (17.7%) had been prescribed statins.

Antihypertensive agents and BP control

At the end of observation, 88.7% of the valsartan add-on group and 12.0% of the control group took an ARB (Table 2). In the valsartan add-on group, the average dose of valsartan was 75.6 ± 44.2 mg day^{-1} (median 80.0 mg day^{-1}, range 20–160 mg day^{-1}). In the control group, the proportion of patients taking ACEIs, α-blockers, β-blockers and loop diuretics increased at the end of observation. In the valsartan add-on group, the proportion of patients taking loop diuretics increased, but that of patients taking ACEIs decreased at the end of observation.

The BP measurements for each group are shown in Figure 1a. BP values in both groups decreased after starting the trial. Changes in BP from the screening period to the follow-up period were from 142.1 ± 18.1/77.9 ± 11.0 mm Hg to 134.5 ± 16.6/74.4 ± 10.2 mm Hg in the control group and from 143.6 ± 15.7/80.1 ± 10.7 mm Hg to 133.2 ± 17.1/74.8 ± 10.5 mm Hg in the valsartan add-on group. Over

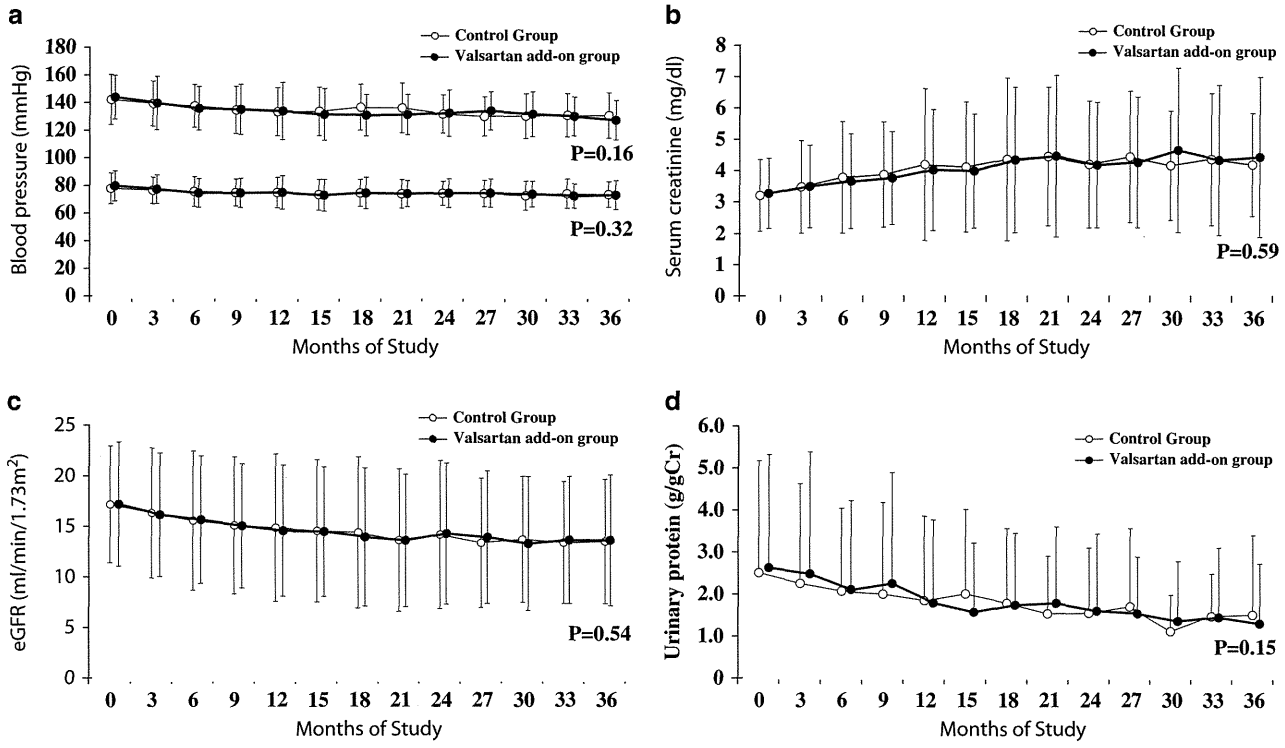


Figure 1 Changes in (**a**) blood pressure, (**b**) serum creatinine, (**c**) estimated glomerular filtration rate (eGFR) and (**d**) urinary protein during the study period.

the course of the study, there was no significant difference in either systolic or diastolic BP values between groups.

Course of renal function

There were gradual increases in serum creatinine levels and gradual decreases in eGFR during the follow-up period in both groups (Figures 1b and c). There were no significant between-group differences in the course of serum creatinine and eGFR changes. However, the mean annual serum creatinine slope from baseline to the end of observation or the two clinical end points was significantly lower in the valsartan add-on group ($1.62 \pm 1.97\,mg\,dl^{-1}$ per year) than in the control group ($2.60 \pm 4.16\,mg\,dl^{-1}$ per year; $P = 0.008$). The mean annual rate of decline in eGFR tended to be lower in the valsartan add-on group ($3.66 \pm 4.48\,ml\,min^{-1}$ per $1.73\,m^2$ per year) than in the control group ($5.20 \pm 10.27\,ml\,min^{-1}$ per $1.73\,m^2$ per year), but the difference was not significant.

Changes in urinary protein

The amounts of urinary protein declined gradually during the follow-up period in both groups (Figure 1d). Levels of proteinuria were log-transformed before analysis to reduce skewness, and there were no significant between-group differences in the changes in urinary protein levels.

Renal and cardiovascular events

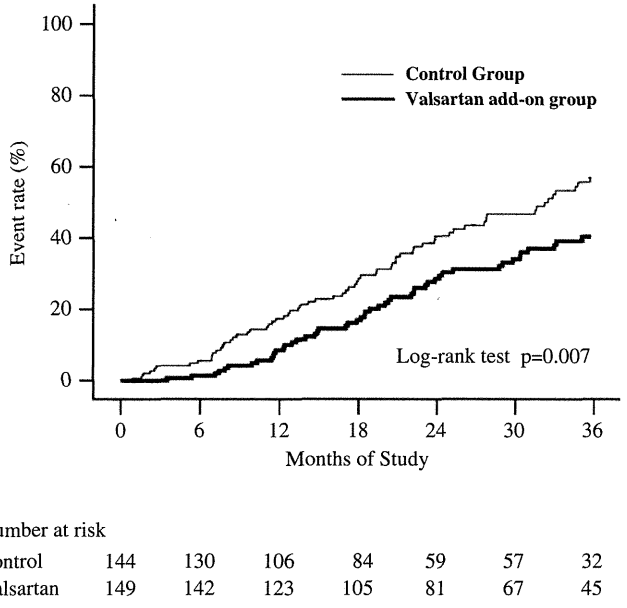
The pre-specified events for patients in both groups are summarized in Table 3. The number of patients who developed ESRD was 106 (36.2%). Mean serum creatinine levels at the time of initiation of maintenance RRT were $9.05 \pm 2.7\,mg\,dl^{-1}$ in the control group and $9.06 \pm 3.14\,mg\,dl^{-1}$ in the valsartan add-on group, with no significant differences between groups. The proportion of patients who reached the cardiovascular end points was very low: 9 (6.3%) in the control group and 9 (6.0%) in the valsartan add-on group. The rate of death from any cause was also very low, with only three deaths occurring (1.0%), two from heart failure and one from ischemic colitis.

Table 3 Incidence of end points and adverse events

	Control (n = *144*)	*Valsartan* (n = *149*)
Doubling of sCr	49 (34.0)	24 (22.8)
ESRD	60 (41.7)	46 (30.9)
Stroke	2 (1.4)	2 (1.3)
Ischemic heart disease	0 (0)	2 (1.3)
Other vascular disease	2 (1.4)	2 (1.3)
Heart failure	5 (3.5)	3 (2.0)
Death	2 (1.4)	1 (0.7)
Hypotension	1 (0.7)	4 (2.7)
Hyperkalemia	0 (0)	1 (0.7)
Infection	1 (0.7)	3 (2.0)
Malignancy	0 (0)	2 (1.3)
Other adverse events	2 (1.4)	2 (1.3)

Abbreviations: ESRD, end-stage renal disease; sCr, serum creatinine.
Data are expressed as number (percentage) of patients.

Because there were small numbers of cardiovascular events, the intention was to explore the effect of valsartan on renal events. The proportions of patients in each group who reached the renal end point, defined as a doubling of the serum creatinine level or ESRD, are shown in Figure 2. There was a significant decrease in the renal event rate in the valsartan add-on group compared with that in the control group ($P = 0.007$). Renal events were reached in 70 (48.6%) patients in the control group and 53 (35.6%) patients in the valsartan add-on group. Patients in the valsartan add-on group had a 38.3% unadjusted relative risk reduction of reaching the renal end point (95% confidence interval: 11.9–56.9%; $P = 0.008$). After adjustment



Number at risk							
Control	144	130	106	84	59	57	32
Valsartan	149	142	123	105	81	67	45

Figure 2 Kaplan–Meier curve of the percentage of patients with a doubling of the serum creatinine or end-stage renal disease (ESRD).

for baseline variables, including sex, age, body mass index, coexistence of diabetes mellitus, ischemic heart disease, dyslipidemia, systolic BP ($\geqslant$140 mm Hg), serum creatinine group and urinary protein group, the decrease in risk with the addition of valsartan remained unchanged (42.6, 95% confidence interval: 16.4–60.6%; $P=0.004$; Table 4). Other significant baseline factors that correlated with renal events were serum creatinine, urinary protein and systolic BP level.

Adverse events

In addition to the three deaths, a small number of adverse events were observed (Table 3). The number of patients in whom adverse events occurred during the study period was almost the same in both groups. There were no serious adverse events that required stopping the study.

DISCUSSION

Whether the addition of valsartan, at a flexible dose according to BP, prevents the progression of CKD better than conventional treatment without an ARB was examined in Japanese patients with hypertension and advanced CKD. Although there was no difference in the course of renal function between the two study groups, the rate of renal events was significantly decreased in the valsartan add-on group.

In this study, ~36% of participants had progressed to ESRD during the study. Because patients with higher serum creatinine levels had withdrawn earlier from the study, it is likely that the changes in serum creatinine or eGFR do not accurately reflect the course of renal function. Therefore, the mean annual serum creatinine slope from the baseline to the last measurement was also examined in each patient. The results showed that the mean annual slope of serum creatinine was significantly lower in the valsartan add-on group than in the control group. The mean annual rate of decline in eGFR was also lower in the valsartan add-on group. Thus, the lack of difference in the course of renal function is possibly due to survival bias. Furthermore, no difference in the course of serum creatinine between groups might reflect the favorable effects of the addition of valsartan on the course of renal function because larger numbers of patients in

Table 4 Results of Cox proportional hazard models for the renal events

Variables	*HR (95% CI)*	P-*value*
Valsartan add-on *vs.* control	0.57 (0.39–0.84)	0.004
Gender		
Male *vs.* female	0.65 (0.40–1.04)	0.072
Age		
(+1 year)	1.00 (0.99–1.02)	0.639
BMI		
(+1 kg m^{-2})	1.02 (0.99–1.08)	0.582
Diabetes mellitus	1.45 (0.95–2.20)	0.086
Ischemic heart disease	0.96 (0.54–1.70)	0.890
Dyslipidemia	0.76 (0.52–1.13)	0.176
Smoking habit	1.14 (0.72–1.81)	0.582
SBP (mm Hg)		
$\geqslant$140 *vs.* <140	1.61 (1.07–2.43)	<0.001
sCr (mg dl^{-1})		
$\geqslant$3.0 to <4.0 *vs.* $\geqslant$2.0 to <3.0	2.14 (1.35–3.40)	0.001
$\geqslant$4.0 *vs.* $\geqslant$2.0 to <3.0	7.03 (4.35–11.4)	<0.001
UP (g gCr^{-1})		
$\geqslant$1.0 to <3.5 *vs.* <1.0	1.66 (1.04–2.67)	0.036
$\geqslant$3.5 *vs.* <1.0	4.50 (2.49–8.13)	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SBP, systolic blood pressure; sCr, serum creatinine; UP, urinary protein.

the control group with high serum creatinine reached ESRD earlier and were excluded from subsequent analyses.

The validity of the above assumption is verified by the finding that there was a 43% decrease in the adjusted hazard ratio of the rate of renal events, defined as a doubling of serum creatinine or development of ESRD, in the valsartan add-on group compared with the conventional treatment group without ARB. Numerous randomized clinical trials in Western countries have demonstrated the benefit of ACEIs or ARBs in slowing CKD progression in patients with diabetes and non-diabetes.[9–12] The reduction of renal events in the present study was comparable with these previous studies. Therefore, the present study indicates that the addition of an ARB, valsartan, also slows renal disease progression to ESRD in Japanese patients with advanced CKD.

In addition to the add-on valsartan, levels of BP, serum creatinine and proteinuria were also significant factors influencing the progression of CKD in the present study. There is growing evidence that the major risk factors for renal disease progression are levels of BP, proteinuria and GFR.[13–18] In addition, it is well known that small changes in BP during the course of a study can significantly affect the rate of CKD progression.[15] BP levels were well controlled and remained similar in both groups throughout this trial.

With respect to proteinuria, previous studies demonstrated that RAS inhibitors provide superior renoprotection in subjects with high urinary protein excretion.[2,14,18] In the present study, the proportion of patients with urinary protein <0.3 g day^{-1} was only 11.3%. Therefore, it is likely that the significant reduction of renal events observed in the present study was because of the high proportion of participants with overt proteinuria. However, there were no between-group differences in urinary protein levels during the trial. Previous

studies have demonstrated that the degree of reduction in proteinuria parallels the reduction of renal events.[9,17,18] Many studies have confirmed the association between the severity of proteinuria and the progression of CKD.[9,18] Therefore, in the present study, a larger number of patients with a high level of proteinuria in the control group might have reached ESRD earlier and been excluded from subsequent analyses of proteinuria. As a result, proteinuria reduction with ARBs may be masked. Further analyses are needed to determine the renal protective effect of valsartan and the relationship between the reduction of urinary protein and the progression of kidney disease.

CKD patients are at greater risk for adverse cardiovascular events than developing ESRD.[19] The rates of cardiovascular events in the present study were lower (~4% or 2.9 cases per 1000 person-years) than previous studies involving patients with advanced CKD, such as the RENAAL study and IDNT. In these studies, the rates were higher by a factor of ~20 or 60 cases per 1000 person-years.[11,12] The reason for this discrepancy is likely a result of the Japanese population generally exhibiting a lower incidence of cardiovascular disease compared with Western countries.[20] Because event rates for cardiovascular disease and death were generally low in the present study, conclusions about the effect of ARB add-on therapy on these outcomes cannot be definitive.

Notably, approximately half of the participants in the conventional group and approximately a quarter of those in the valsartan add-on group were taking ACEIs in the present study. The recent results regarding combination ACEI and ARB therapy in the ONTARGET report are opposite those of the present study.[21] However, the backgrounds of participants differ between the two studies, as the ONTARGET study involved patients with almost normal GFR and without massive proteinuria. In addition, the manner of dose escalation was different. In the ONTARGET study, the dose was increased on a regular basis with a predetermined fixed amount. On the other hand, in the present study, valsartan was started from half of the usual dose and increased gradually, adjusted in an appropriate manner according to the patient's condition, considering changes in BP, proteinuria, renal function and serum potassium levels by well-trained nephrologists. It seems mandatory in the management of CKD to decide the dose and dose escalation of antihypertensive drugs, including ARBs, according to the condition and course of each individual patient, with close monitoring of serum creatinine, serum potassium, BP and urinary protein. Although there were higher incidences of hypotension and hyperkalemia in the valsartan add-on group, the overall incidence of adverse events was very small. Therefore, an ARB can be safely used in hypertensive patients with advanced CKD under careful observation of the condition and clinical course of the patients.

Recently, several studies reported differences in renal effects between subtypes of calcium channel blockers.[22–24] In particular, N/L-type and T/L-type calcium channel blockers with or without RAS inhibitors have favorable effects on the kidney in patients with CKD, including reduction of proteinuria. In this study, 80% of participants took various calcium channel blockers. Therefore, further study is necessary to elucidate the differences of effects between subtypes of calcium channel blockers and the renoprotective effects of valsartan in patients with advanced predialysis CKD.

This study had several limitations. First, as this study was not a double-blind study, the results may be affected by unexpected confounders. Second, although all reported events were checked by the safety and clinical event committee, all events were reported by the attending physician, and hence minor side effects were likely missed. However, the finding of no difference in mean serum creatinine levels at the time of the initiation of RRT between the two groups supports the notion that the initiation of RRT was performed objectively. Third, the present study was not designed to define the optimal target BP with antihypertensive treatment in patients with advanced CKD. Further studies are needed to determine the optimal BP goal for advanced CKD. Finally, this study was performed at institutions with well-trained nephrologists and highly regarded programs for patients with CKD. Therefore, generalization of the results of the present study to patients managed by general physicians is difficult. Consultation with nephrologists is strongly recommended for the management of patients with advanced predialysis CKD.

This study demonstrated that the addition of an ARB, valsartan, to conventional treatment slowed the rate of renal function decline and delayed the need for RRT. ARBs might exert superior renoprotection compared with conventional treatment alone in Japanese hypertensive patients with advanced CKD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)

Supplementary information

KVT study organization and investigators

KVT study organization

Executive committee: Kenjiro Kimura (St. Marianna University), Satoshi Umemura (Yokohama City University), Masayuji Endo (Tokai University), Terukuni Ideura (Showa University), Kouju Kamata (Kitasato University)

Steering committee: Asio Yoshimura (Showa University), Takashi Yasuda (St. Marianna University), Yoshiyuki Toya (Yokohama City University), Daisuke Suzuki (Tokai University), Yasushi Nagaba (Kitasato University), Takeo Sato (Kawasaki Municipal Tama Hospital)

Safety & event committees: Akihisa Tanabe (Tokai University), Osamu Tochikubo (Yokohama City University), Takashi Masuda (Kitasato University)

Statistical analysis advisor: Shinobu Tatsunami (St. Marianna University)

Clinical trial center: Yuzou Takamori (East Asia Trading)

KVT study investigators

Terukuni Ideura (Showa University Fujigaoka Hospital), Takeo Sato (Kawasaki Municipal Tama Hospital), Takashi Yasuda (St. Marianna University Hospital), Kenjiro Kimura (St. Marianna University Hospital), Gen Yasuda (Yokohama City University Medical Center), Hiroyuki Morita (Showa University Fujigaoka Hospital), Masao Toyota (Tokai University Hospital), Kouichi Tamura (Yokohama City University Hospital), Masayuki Endo (Tokai University Hospital), Shigeki Iwasaki (Toshiba Rinkan Hospital), Kouju Kamata (Kitasato University Hospital), Yumiko Kikeda (Yokohama Minami Kyosai Hospital), Kouzou Tamura (Yamato Municipal Hospital), Nobuhito Hirawa (Yokohama City University Medical Center), Shingo Kuboshima (St. Marianna University Hospital), Tomoya Fujino (St. Marianna University Hospital), Daisaku Ando (Yokohama City University Medical Center), Tetsuya Fujikawa (Yokohama Minami Kyosai Hospital), Yoshiyuki Toya (Yokohama City University Hospital), Junji Yamauchi (Yokohama City University Hospital),

Makoto Nishina (Tokai University Hospital), Rika Morita (Kitasato University Hospital), Sumi Ueno (Yokohama Seamen's Insurance Hospital), Naoyuki Kobayasi (Soubudai Nieren Clinic), Yoshinori Shima (St. Marianna University Hospital), Sayuri Shirai (St. Marianna University Hospital), Yusuke Konno (St. Marianna University Hospital), Daisuke Suzuki (Tokai University Hospital), Tomoya Umezono (Tokai University Hospital), Yoko Koike (Tokai University Hospital), Yasushi Nagaba (Kitasato University Hospital), Takashi Sano (Kitasato University Hospital), Syoukichi Naito (Kitasato University Hospital), Aya Kitamura (Yokohama Minami Kyosai Hospital), Satoshi Umemura (Yokohama City University Hospital), Kei Matsushita (Yokohama City University Hospital), Masashi Sakai (Yokohama City University Hospital), Toshiharu Kokuho (Yokohama City University Hospital), Kousaku Iwatsubo (Yokohama City University Hospital), Tsutomu Watanabe (Showa University Fujigaoka Hospital), Satoshi Kondo (St. Marianna University Yokohama City Seibu Hospital), Mitsunori Yagame (Tokai University Hospital), Masashi Honma (Tokai University Hospital), Takao Suga (Tokai University Oiso Hospital), Hisato Sakamoto (Kitasato University Hospital), Mineko Kanemitsu (Kitasato University Hospital), Tougo Aoyama (Kitasato University Hospital), Masanori Aoyama (Kitasato University Hospital)

Usefulness of Urinary Biomarkers in Early Detection of Acute Kidney Injury After Cardiac Surgery in Adults

Katsuomi Matsui, MD, PhD; Atsuko Kamijo-Ikemori, MD, PhD; Takeshi Sugaya, PhD; Takashi Yasuda, MD, PhD; Kenjiro Kimura, MD, PhD

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ORIGINAL ARTICLE
Renal Disease

Usefulness of Urinary Biomarkers in Early Detection of Acute Kidney Injury After Cardiac Surgery in Adults

Katsuomi Matsui, MD, PhD; Atsuko Kamijo-Ikemori, MD, PhD; Takeshi Sugaya, PhD; Takashi Yasuda, MD, PhD; Kenjiro Kimura, MD, PhD

Background: Acute kidney injury (AKI) is a common complication after cardiac surgery. Urinary liver-type fatty acid-binding protein (L-FABP) reflects the presence of renal tubular injury. The aim of the present study was to evaluate the utility of urinary L-FABP compared with other urinary biomarkers for the early detection of postoperative AKI among adult patients undergoing cardiac surgery.

Methods and Results: Patients were divided into the AKI (n=48) and non-AKI groups (n=37) according to whether they developed postoperative AKI within 48 h after surgery. Changes in various biomarkers were evaluated. Urine and serum samples were obtained from each patient at the following time points: before the operation, immediately after the operation, and 3, 6, 18, 24, and 48 h postoperatively. The urinary L-FABP level was significantly higher in the AKI group than in the non-AKI group at every time point, while other biomarkers did not show such a tendency. The biomarker with the largest area under the curve at every time point for predicting the onset of AKI was urinary L-FABP. On multiple logistic regression analysis, the urinary L-FABP level before operation and within the first 6 h after cardiac surgery was significantly associated with the onset of AKI.

Conclusions: Urinary L-FABP is a useful biomarker for early detection of AKI and is a good early predictor of the onset of AKI. (*Circ J* 2012; **76:** 213–220)

Key Words: Acute kidney injury; Cardiac surgery; Liver-type fatty acid-binding protein

Acute kidney injury (AKI) is a common complication of critically ill patients and patients who have undergone cardiac surgery, and is associated with increased morbidity and mortality.[1,2] In adults, AKI has been reported to complicate 1–7% of all hospital admissions[3,4] and be a complication in 5–47% of patients who undergo cardiac surgery.[1,5] Despite progress in the understanding of the pathophysiologic mechanisms of AKI, as well as progress in the general care of patients with AKI, the mortality rate of AKI in the intensive care unit setting remains at 50–70%, with a significant number of survivors with deteriorated renal function.[6,7] In order to detect AKI at the early stage and to be able to provide interventions promptly, the Acute Dialysis Quality Initiative developed the RIFLE criteria for diagnosis of acute renal failure in critically ill patients,[8] and the Acute Kidney Injury Network (AKIN) developed the AKIN criteria for diagnosis of AKI.[9] Both of these definitions incorporate elevation in serum creatinine (SCr) or occurrence of oliguria as alternative criteria of AKI. Indeed, AKI is identified by increases in SCr measured over time in clinical practice. SCr, however, is widely known to be a suboptimal marker after renal injury in that its level often does not reflect the glomerular filtration rate (GFR) or the degree of tubular injury.[10] Therefore, instead of SCr, new biomarkers for the early diagnosis of AKI, for the stratification of patients with AKI, and for monitoring renal damage after treatment of AKI, are being developed.

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Liver-type fatty acid binding protein (L-FABP) is found in the cytoplasm of human proximal tubular cells.[11] L-FABP binds fatty acids and transports them to mitochondria or peroxisomes, where the fatty acids are β-oxidized, and participates in intracellular fatty acid homeostasis.[12,13] In the clinical setting, urinary L-FABP, which accurately reflects the degree of tubular injury,[14] has been reported to be useful for early detection of AKI in pediatric patients who had undergone cardiac surgery and in adult patients who developed contrast media-induced nephropathy.[15,16] The clinical utility of urinary L-FABP for early detection of AKI in adults after cardiac surgery, however, has not been sufficiently evaluated. The aim of the present study was therefore to evaluate the utility of

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Department of Nephrology and Hypertension, Internal Medicine (K.M., A.K.-I., T.S., T.Y., K.K.), Department of Anatomy (A.K.-I.), St Marianna University School of Medicine, Kanagawa; and CMIC Co Ltd, Tokyo (T.S.), Japan
Mailing address: Kenjiro Kimura, MD, PhD, Department of Nephrology and Hypertension, Internal Medicine, St Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan. E-mail: kimura@marianna-u.ac.jp

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Table 1. Patient Characteristics and Clinical Outcome

	Non-AKI group	AKI group	P value
n	37	48	
Age (years), median (range)	70 (17–86)	73 (36–87)	0.297
Gender (M/F)	30/7	34/14	0.277
Comorbid disease, n (%)			
Diabetes mellitus	15 (40.5)	12 (25.0)	0.127
Hypertension	33 (89.2)	40 (83.3)	0.442
Hyperlipidemia	22 (59.5)	27 (56.3)	0.767
Cardiovascular disease	9 (24.3)	19 (39.6)	0.138
Concomitant medication, n (%)			
RAAS blockade treatment	15 (40.5)	30 (62.5)	0.044
Diuretics	12 (32.4)	27 (56.3)	0.029
Type of operation			0.111
CABG-CPB	3	1	
OPCABG	16	12	
Valve surgery	2	10	
CABG+valve surgery	3	2	
Aneurysm	9	18	
Other	4	5	
BMI (kg/m^2), median (range)	22.8 (15.2–28.5)	21.7 (14.2–32.6)	0.247
Operation time (min), median (range)	420 (185–865)	450 (185–1,290)	0.043
Episode of hypotension during operation (SBP <90 mmHg), n (%)	5 (13.5)	16 (33.3)	0.036
Postoperative characteristics			
Length of CCU stay (days), median (range)	3 (2–15)	6 (2–20)	<0.0005
Length of hospital stay (days), median (range)	25 (12–90)	31.5 (10–70)	0.005
Required renal replacement therapy	0	5	0.066
In-hospital death	0	3	0.254

AKI, acute kidney injury; RAAS, renin-angiotensin-aldosterone system; CABG-CPB, coronary artery bypass grafting with cardiopulmonary bypass; OPCABG, off-pump coronary artery bypass grafting; CABG, coronary artery bypass grafting; BMI, body mass index; SBP, systolic blood pressure; CCU, coronary care unit.

urinary L-FABP compared with other urinary biomarkers for the early detection of AKI among patients who have undergone cardiac surgery.

Methods

Patient Selection

Adult patients undergoing cardiac surgery in the Department of Cardiovascular Surgery, St Marianna University School of Medicine were eligible for enrollment. A total of 85 patients who were admitted to the coronary care unit (CCU) after cardiac surgery were prospectively studied from August 2009 to October 2010. Patients who depended on chronic dialysis support, patients undergoing emergency operation (operation performed within 24 h after admission) and patients who died within the first 24 h after surgery were excluded from this study. Patients were divided into the AKI and non-AKI groups according to whether they developed AKI within 48 h after surgery. Postoperative AKI was defined according to AKIN criteria, which is an absolute increase in SCr of ≥26.4 μmol/L (0.3 mg/dl) from baseline or a relative increase in SCr of >1.5-fold from baseline within the first 48 h after cardiac surgery.[9] The present study was carried out according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients, and the institutional review board approved the study protocol.

Urine and Serum Sample Collection and Storage

Ten milliliters of urine was obtained through the urinary catheter at the following time points from each patient: before the operation, immediately after the operation, and 3, 6, 18, 24, and 48 h postoperatively. Serum samples were obtained at the same time points as urine collection and the SCr levels were determined. The urine samples were centrifuged at 1,000 g at 4°C for 5 min and the supernatants were stored at –80°C until analysis.

Enzyme-Linked Immunosorbent Assay for Measurement of Urinary L-FABP and Neutrophil Gelatinase-Associated Lipocalin

The level of urinary L-FABP was measured on enzyme-linked immunosorbent assay (ELISA) using the Human L-FABP ELISA kit (CMIC, Tokyo, Japan).[17] The level of urinary neutrophil gelatinase-associated lipocalin (NGAL) was measured using the NGAL Rapid ELISA Kit (BioPorto, Gentofte, Denmark).[18]

Biomarker Measurements in Blood and Urine

Serum creatinine, urinary creatinine, urinary albumin, and urinary *N*-acetyl-β-D-glucosaminidase (NAG) levels were measured. The levels of urinary biomarkers are expressed as a ratio of the level of urinary creatinine.

Statistical Analysis

Results are expressed as median (range or 25–75% interquartile range) or mean±SEM. To compare 2 groups, the Mann–Whitney U-test was used for unpaired data. Categorical variables were compared using chi-square test. Differences among the same group were analyzed using 1-way analysis of variance

Table 2. Changes in Biomarkers vs. Presence of AKI

	Non-AKI group	AKI group	P value
Serum Cr (mg/dl)			
Before operation	0.78 (0.72–0.98)	0.92 (0.76–1.14)	0.06
Immediately after	0.81 (0.69–0.95)	1.01 (0.82–1.28)	0.001
3 h	0.82 (0.68–1.00)	1.11 (0.95–1.44)	0.001
6 h	0.76 (0.69–0.99)	1.19 (1.05–1.33)	<0.0005
18 h	0.83 (0.74–1.00)	1.21 (0.99–1.46)	<0.0005
24 h	0.80 (0.71–0.95)	1.23 (1.08–1.56)	<0.0005
48 h	0.79 (0.70–0.94)	1.40 (1.02–1.64)	<0.0005
Urinary L-FABP (μg/gCr)			
Before operation	5.67 (2.74–8.21)	11.19 (7.15–24.35)	<0.0005
Immediately after	19.80 (9.36–38.11)	244.04 (69.45–1,009.73)	<0.0005
3 h	21.41 (9.77–52.63)	182.49 (61.13–773.82)	<0.0005
6 h	13.63 (7.23–29.67)	106.05 (28.29–480.67)	<0.0005
18 h	23.98 (14.78–35.21)	67.23 (34.10–137.54)	<0.0005
24 h	20.66 (15.24–26.96)	39.44 (24.58–96.85)	<0.0005
48 h	17.71 (12.39–23.45)	33.66 (18.54–51.30)	0.0006
Urinary NGAL (μg/gCr)			
Before operation	5.15 (0–13.43)	18.45 (0–86.98)	0.003
Immediately after	53.50 (27.50–160.0)	137.2 (52.65–272.78)	0.12
3 h	36.3 (23.80–72.70)	121.25 (39.58–39.09)	0.01
6 h	22.0 (7.30–50.50)	76.65 (31.50–201.68)	<0.0005
18 h	26.0 (8.0–46.1)	72.95 (24.85–218.39)	<0.0005
24 h	21.9 (11.3–37.9)	59.1 (29.1–194.25)	<0.0005
48 h	23.4 (10.3–47.3)	41.21 (21.63–100.18)	0.03
Urinary albumin (mg/gCr)			
Before operation	34.3 (20.50–70.37)	85.80 (27.05–216.30)	0.03
Immediately after	46.72 (23.58–100.49)	104.70 (34.58–213.12)	0.009
3 h	26.05 (17.88–58.68)	114.90 (41.45–211.50)	<0.0005
6 h	22.36 (13.90–36.40)	58.80 (30.02–133.50)	<0.0005
18 h	18.85 (12.57–31.55)	56.90 (23.88–103.65)	<0.0005
24 h	23.40 (13.00–31.90)	58.89 (22.78–132.88)	<0.0005
48 h	26.90 (15.75–41.20)	41.75 (26.50–99.11)	0.004
Urinary NAG (U/gCr)			
Before operation	12.69 (6.88–17.69)	14.63 (7.82–30.64)	0.08
Immediately after	26.32 (14.50–50.22)	38.16 (24.05–65.99)	0.053
3 h	20.17 (12.97–35.51)	32.65 (17.70–50.37)	0.02
6 h	12.87 (5.34–16.47)	19.08 (11.36–29.89)	0.004
18 h	11.16 (7.99–16.96)	18.39 (12.43–36.69)	0.001
24 h	14.35 (8.15–23.56)	24.80 (18.39–41.05)	<0.0005
48 h	20.12 (9.65–32.11)	26.40 (16.88–41.84)	0.04

Data of parameters expressed as median (25–75% interquartile range).
AKI, acute kidney injury; Cr, creatinine; L-FABP, liver-type fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-glucosaminidase.

followed by Dunnett test. Receiver-operating characteristic curves (ROCs) for clinical parameters were plotted to predict the onset of AKI. We then assessed the ability of urinary biomarkers to predict the onset of AKI by calculating the area under the ROC (AUC). An AUC of 0.90–1.0 indicated excellent, 0.80–0.89, good; 0.70–0.79, fair; 0.60–0.69, poor; and 0.50–0.59, no useful value. The sensitivity, specificity, positive predictive value and negative predictive value were calculated from 2×2 contingency tables. Multivariate logistic regression analysis was performed to determine risk factors for the onset of AKI. Statistical analysis was performed using SPSS for Windows 15.0 (SPSS, Chicago, IL, USA) and Stat Flex Version 6.0 (Artec, Osaka, Japan). $P<0.05$ was considered to be statistically significant.

Results

Patient Characteristics

This study included 85 patients who were admitted to the CCU after cardiac surgery. Forty-eight patients (56%) developed AKI within the first 48 h after cardiac surgery and were placed in the AKI group, while the remaining 37 patients did not and were placed in the non-AKI group. The characteristics of the AKI and non-AKI groups are listed in **Table 1**. As to the severity (stage) of AKI judged according to the AKIN criteria, 39 patients developed stage 1, 4 patients developed

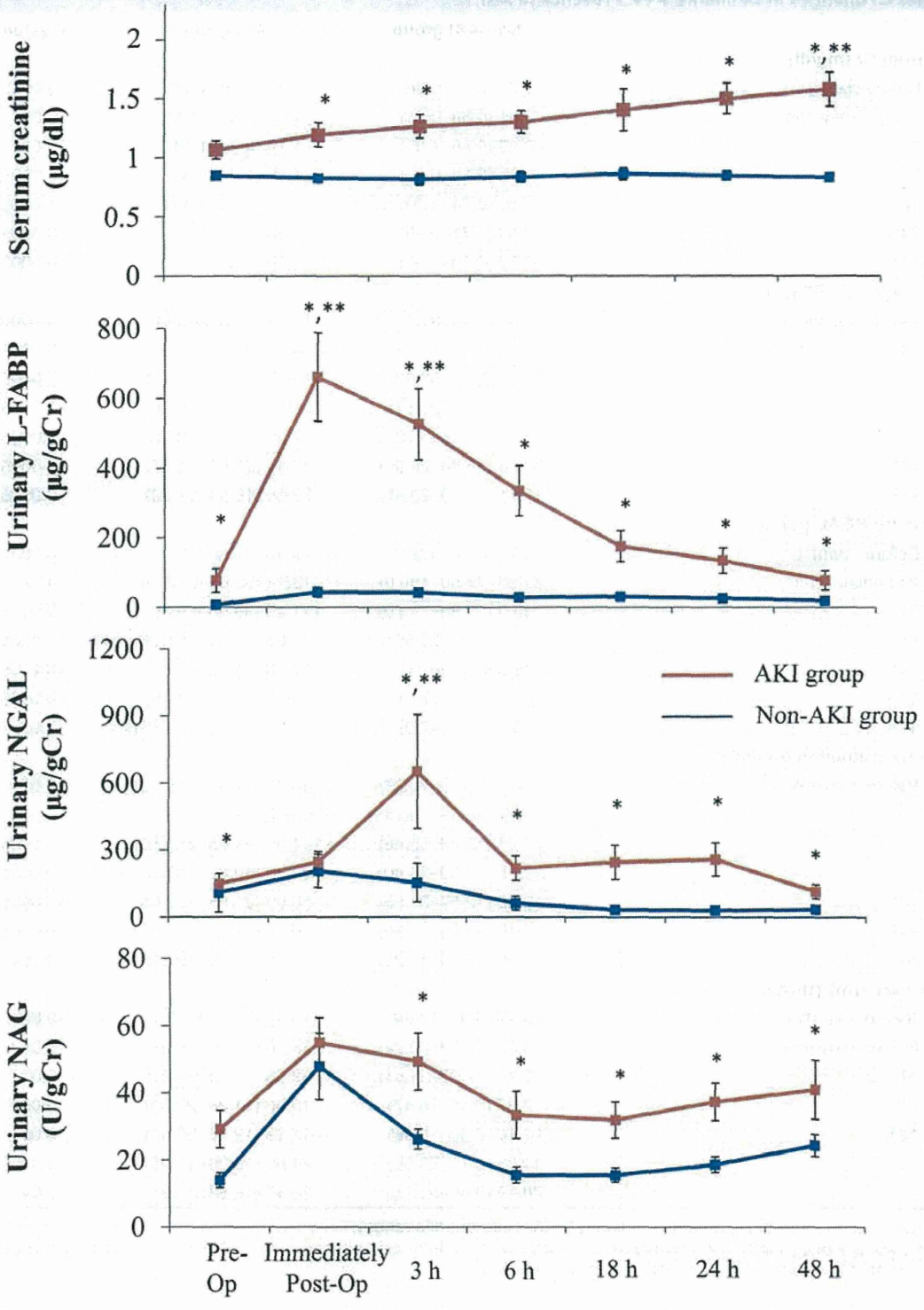

Figure. Changes in various urinary parameters in the (red) acute kidney injury (AKI) and (blue) non-AKI groups. Pre-Op, preoperative value; Immediately post-op, immediately postoperative value. *P<0.05, compared with the non-AKI group at the same time point; **P<0.05 compared with the respective preoperative level in the same group. L-FABP, liver-type fatty acid-binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.

stage 2 and 5 patients developed stage 3. Five patients in the AKI group required continuous renal replacement therapy. Three patients in the AKI group died in the hospital. With respect to age, gender, comorbid diseases and body mass index (BMI), no differences were noted between the AKI and non-AKI groups (**Table 1**). As to concomitant medications such as renin-angiotensin-aldosterone system (RAAS) blockade treatment and diuretics before operation, significantly higher percentages of patients in the AKI group were taking these medications compared with the non-AKI group (P=0.044 and P=0.029, respectively; **Table 1**). The operation time was significantly longer in the AKI group than in the non-AKI group (P=0.043). The length of CCU stay and length of hospital stay were significantly longer in the AKI group than in

Table 3. AUC vs. Time

	Time after operation						
	Before operation	Immediately after	3 h	6 h	18 h	24 h	48 h
Urinary L-FABP	0.80 (0.68–0.92)	0.86 (0.78–0.94)	0.85 (0.77–0.93)	0.83 (0.74–0.91)	0.76 (0.65–0.87)	0.78 (0.68–0.88)	0.75 (0.62–0.88)
Urinary NGAL	0.72 (0.59–0.86)	0.60 (0.47–0.72)	0.68 (0.56–0.80)	0.74 (0.63–0.85)	0.73 (0.63–0.84)	0.77 (0.67–0.86)	0.64 (0.52–0.76)
Urinary albumin	0.66 (0.53–0.80)	0.67 (0.55–0.78)	0.77 (0.67–0.87)	0.74 (0.63–0.85)	0.75 (0.65–0.86)	0.75 (0.65–0.86)	0.69 (0.58–0.81)
Urinary NAG	0.63 (0.49–0.77)	0.63 (0.50–0.75)	0.65 (0.53–0.76)	0.68 (0.57–0.80)	0.71 (0.60–0.82)	0.73 (0.62–0.84)	0.64 (0.51–0.77)

Data given as AUC (95% confidence interval).
AUC, area under the curve. Other abbreviations see in Table 2.

the non-AKI group (P<0.0005 and P=0.005, respectively).

Urinary Parameters and Renal Function

Changes in various parameters in the AKI and non-AKI groups are shown in **Table 2** and **Figure**. Although there was no difference in the SCr level between the 2 groups prior to operation, the SCr level was significantly higher in the AKI group than in the non-AKI group up to and including 48 h after surgery. The urinary L-FABP level in the AKI group was significantly higher than that in the non-AKI group before operation and up to and including 48 h after the surgery. In the AKI group, the urinary L-FABP level was significantly higher immediately after operation and at 3 h after the surgery compared with the respective level before operation. The urinary NGAL level was significantly higher in the AKI group than in the non-AKI group before operation and up to and including 48 h after the surgery except at immediately after the operation. In addition, in the AKI group, there was no difference in urinary NGAL level between the preoperative level and the immediately postoperative level. The urinary albumin level was significantly higher in the AKI group than in the non-AKI group at all time points. In the AKI group, there were no differences in urinary albumin level between the preoperative level and the level at each time point after the surgery. The urinary NAG level was significantly higher in the AKI group than in the non-AKI group at 3 h after the operation. In the AKI group, there were no differences in urinary NAG between the preoperative level and the level at each time point after the surgery.

ROC Analysis of Urinary Biomarkers for Predicting Onset of AKI

The biomarker with the largest AUC for predicting the onset of AKI was urinary L-FABP at all time points (**Table 3**). Before operation, immediately after the operation, and 3, 6, 18, 24, and 48 h after the surgery, the AUCs for predicting the onset of AKI in urinary L-FABP were 0.80, 0.86, 0.85, 0.83, 0.76, 0.78, and 0.75, respectively – the largest AUC for predicting the onset of AKI being at immediately after the operation. Within the first 6 h after cardiac surgery, namely the early time points after the operation, the AUCs of urinary L-FABP were >0.80 at each time point. These results suggest that urinary L-FABP is a good early predictor of the onset of AKI after cardiac surgery.

Logistic Regression Analysis for Prediction of Onset of AKI

We performed multiple logistic regression analysis using the

Table 4. Logistic Regression Analysis for Renal Biomarkers and Patient Characteristics

	OR	95%CI	P value
Before operation			
Urinary L-FABP (10 μg/gCr)	3.739	1.133–12.335	0.03
Urinary NGAL (μg/gCr)	0.999	0.995–1.002	0.39
Urinary NAG (U/gCr)	1.025	0.971–1.082	0.377
Urinary albumin (mg/gCr)	1.003	0.997–1.010	0.277
Age (years)	1.041	0.956–1.132	0.355
Sex (M/F)	0.905	0.210–3.901	0.894
BMI (kg/m^2)	1.074	0.807–1.429	0.627
eGFR (ml·min^{-1}·1.73 m^{-2})	0.985	0.945–1.026	0.461
Arrival in the CCU			
Urinary L-FABP (100 μg/gCr)	2.947	1.321–6.576	0.008
Urinary NGAL (μg/gCr)	0.998	0.996–1.001	0.235
Urinary NAG (U/gCr)	1.003	0.989–1.017	0.711
Urinary albumin (mg/gCr)	1.001	0.999–1.004	0.252
Age (years)	1.016	0.961–1.074	0.566
Sex (M/F)	0.812	0.161–4.090	0.801
BMI (kg/m^2)	1.010	0.791–1.290	0.935
Operation time (min)	1.002	0.997–1.006	0.443
3 h after operation			
Urinary L-FABP (100 μg/gCr)	3.485	1.263–9.612	0.016
Urinary NGAL (μg/gCr)	0.998	0.996–1.001	0.188
Urinary NAG (U/gCr)	1.009	0.981–1.039	0.515
Urinary albumin (mg/gCr)	1.011	0.998–1.025	0.098
Age (years)	1.006	0.958–1.056	0.820
Sex (M/F)	0.326	0.049–2.181	0.248
BMI (kg/m^2)	1.031	0.795–1.335	0.820
Operation time (min)	1.004	0.999–1.010	0.142
6 h after operation			
Urinary L-FABP (100 μg/gCr)	5.571	1.426–21.758	0.013
Urinary NGAL (μg/gCr)	0.999	0.995–1.002	0.449
Urinary NAG (U/gCr)	1.012	0.977–1.049	0.507
Urinary albumin (mg/gCr)	1.009	0.997–1.021	0.128
Age (years)	1.011	0.966–1.062	0.646
Sex (M/F)	1.342	0.333–5.408	0.679
BMI (kg/m^2)	0.901	0.725–1.119	0.345
Operation time (min)	1.003	0.999–1.008	0.170

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate. Other abbreviations see in Tables 1–3.

Table 5. Predictive Value of Urinary L-FABP for Diagnosis of AKI

Time point	Cut-off value (μg/gCr)	Sensitivity	Specificity	PPV	NPV
Before operation	6.96	0.76	0.68	0.78	0.65
Immediately after	54.59	0.77	0.92	0.93	0.75
3h	68.35	0.74	0.83	0.85	0.71
6h	21.22	0.83	0.72	0.8	0.76
18h	36.33	0.74	0.82	0.85	0.7
24h	28.77	0.69	0.78	0.8	0.65
48h	25.8	0.59	0.87	0.87	0.59

PPV, positive predictive value; NPV, negative predictive value. Other abbreviations see in Tables 1,3.

patient characteristics and urinary biomarkers measured at each time point. Multiple logistic regression analyses incorporating age, sex, BMI, operation time, and 4 urinary biomarkers (L-FABP, NGAL, albumin, and NAG) measured immediately after operation, at 3 h postoperatively, or at 6 h postoperatively showed that urinary L-FABP was the only predictor that was significantly associated with the onset of AKI (P=0.008, odds ratio [OR], 2.947, 95% confidence interval [CI]: 1.321–6.576; P=0.016, OR, 3.485, 95%CI: 1.263–9.612; P=0.013, OR, 5.571, 95%CI: 1.426–21.758, respectively; **Table 4**).

Moreover, at the preoperation time point, multiple logistic regression analysis incorporating estimated GFR (eGFR) and the variables listed in the previous section showed that urinary L-FABP was the only predictor that was significantly associated with the onset of AKI (P=0.03, OR, 3.739; 95%CI: 1.133–12.335; **Table 4**).

Urinary L-FABP as a Biomarker for Early Detection of AKI

Because urinary L-FABP was the only predictor that was significantly associated with the onset of AKI (**Table 4**), we determined the cut-off value of urinary L-FABP at each time point (**Table 5**).

Discussion

In this prospective study of 85 adult patients who underwent cardiac surgery, we report 4 notable findings. First, although there was no difference in the preoperative SCr level between the AKI group and non-AKI group, the preoperative urinary L-FABP, urinary NGAL, and urinary albumin levels were significantly higher in the AKI group than in the non-AKI group. Second, the urinary L-FABP level was significantly higher in the AKI group than in the non-AKI group at every time point, while other parameters did not show such a tendency. Moreover, in the AKI group, the urinary L-FABP level was significantly higher up to and including 3 h after the operation compared with the preoperative level. Third, the biomarker with the largest AUC at every time point for predicting the onset of AKI was urinary L-FABP. Especially, within the first 6 h after cardiac surgery, the AUC of urinary L-FABP was >0.80 at each time point. Fourth, on multiple logistic regression using parameters measured at each time point, the urinary L-FABP level before operation and within the first 6 h after cardiac surgery was significantly associated with the onset of AKI. These results suggested that the presence of tubular damage and the deterioration of tubular structure are risk factors for the onset of AKI, and that urinary L-FABP is a useful biomarker for the early detection of AKI and is a good early predictor of the onset of AKI.

L-FABP was recently designated as a new clinical biomarker of tubular damage by the Ministry of Health, Labour and Welfare in Japan. The dynamics of renal L-FABP in kidney disease were determined in many experimental studies of chronic kidney disease or AKI. Renal L-FABP gene expression is upregulated and urinary excretion of L-FABP is increased by various stresses, for example urinary protein overload,[19] tubular ischemia,[20] tubular stretch,[21] hyperglycemia,[22] ischemia/reperfusion,[23] and toxins,[14] which cause tubulointerstitial damage. Tubular stress that causes AKI may upregulate renal L-FABP expression and then accelerate urinary excretion of L-FABP from the proximal tubules. Urinary L-FABP level was significantly associated with the degree of tubulointerstitial damage and increased in accordance with the progression of kidney disease.[14] Therefore, we considered that the urinary L-FABP level may increase before the occurrence of tubular structural damage, may be a useful biomarker for early detection of AKI and may be a real-time indicator of tubulointerstitial damage.

Cardiac surgery changes renal hemodynamics and decreases renal blood flow.[24] The medullary region in the kidney exists on a hypoxic precipice as a result of low blood flow and countercurrent exchange of oxygen, although paradoxically housing nephron segments with very high energy requirements (eg, the S3 segment of the proximal tubule). The ischemic state after cardiac surgery worsens the relative hypoxia, leading to prolonged cellular injury and cell death in these predisposed tubule segments.[25] In the pathogenesis of AKI after cardiac surgery, tubulointerstitial damage provoked by ischemia/reperfusion is an important factor that leads to the onset of AKI.[25,26] Because L-FABP is expressed in cells lining the straight portion of the proximal tubules (S3 segment) in addition to S1 and S2 segments of the proximal tubules within the kidney, renal L-FABP gene expression and urinary excretion of L-FABP from the proximal tubules may be susceptible to increase in accordance with the ischemic state after cardiac surgery. The urinary L-FABP level was significantly higher in the AKI group than in the non-AKI group at every time point, while other parameters did not show such a tendency in this study. The presence of tubulointerstitial damage before cardiac surgery and the strong induction of tubulointerstitial damage after the surgery were associated with the onset of AKI. The urinary L-FABP level precisely reflects such pathophysiology of AKI.

When is the most suitable time for measurement of urinary L-FABP for early detection of AKI in adult patients who undergo cardiac surgery? The highest urinary L-FABP level among the measured time points in the AKI group, the largest AUC of urinary L-FABP for predicting the onset of AKI and the lowest P-value of urinary L-FABP that was independently associated with the onset of AKI, were seen in the urine sample obtained immediately after operation. Measurement of urinary L-FABP immediately after cardiac surgery may help physi-

cians predict the onset of AKI, guide appropriate care and prevent the progression to AKI. Moreover, the cut-off value of urinary L-FABP in the urine sample obtained immediately after the operation for predicting the onset of AKI (ie, 54.59 μg/gCr), was considered to be adequate because this was similar to the cut-off for predicting the onset of AKI in patients admitted to the intensive care unit in our previous study.[27] Therefore, we suggest that the optimal timing of measurement of urinary L-FABP for predicting the development of AKI is immediately after operation. In contrast, as a screening tool for patients at high risk for postoperative AKI, preoperative measurement of urinary L-FABP was suboptimal. Although the AUC of preoperative urinary L-FABP for predicting the onset of AKI was lower than that of the postoperative urinary L-FABP within the first 6 h, if patients at high risk for developing AKI are screened using preoperative urinary L-FABP, we might be able to take steps to avoid risk factors for postoperative AKI, such as instituting RAAS blockade treatment, diuretics, and hypotension during the operation (**Table 1**), and we might be able to manage high-risk patients such as patients with metabolic syndrome,[28] diabetes mellitus,[28,29] and anemia[29] more carefully.

Urinary NGAL was reported to be another biomarker for early detection of AKI after cardiac surgery. In a study of children undergoing cardiac surgery,[30] the urinary concentration of NGAL 2 h after surgery was nearly 100% accurate for correctly identifying patients who developed AKI 14–72 h after surgery. In contrast, subsequent studies have not yielded results as robust as those produced in the initial study. In a cohort of adults undergoing cardiac surgery, the best AUC for urinary NGAL concentration was only 0.80 at the time point of 18 h after surgery. Other time points, both immediately after surgery (2 and 12 h) and 24 h after surgery, did not possess diagnostic accuracy as high.[31] In addition, Koyner et al reported that urinary NGAL had AUC-ROCs of between 0.61 and 0.70 at various time points after cardiac surgery in adult patients.[32] Similarly, less robust results were produced in the present study, in which the best AUC for urinary NGAL was 0.77 at the time point of 24 h after surgery.

What is the difference between urinary L-FABP and urinary NGAL for early detection of AKI in adult patients who undergo cardiac surgery? The difference in the pattern of increase of urinary NGAL and urinary L-FABP after cardiac surgery results from differences in the mechanism of urinary secretion. In the AKI setting, various stresses, especially oxidative stress, the presence of tissue hypoxia and tubule ischemia, upregulate renal L-FABP expression, and there is increased secretion (or shedding) of L-FABP from damaged proximal tubular cells into the luminal space of proximal tubules.[33,34] In contrast, under normal conditions, NGAL is filtered by glomeruli and reabsorbed by proximal tubules, leaving only 0.1–0.2% in the urine.[35] In the AKI setting, first, various stresses increase serum NGAL in the circulation, which induces activation of neutrophils, and then, an increased amount of NGAL is filtered from the glomerular filtrate. Some NGAL molecules are reabsorbed by the damaged proximal tubules while others are excreted. Therefore, increased urinary NGAL is mainly due to impaired renal reabsorption,[36] and it takes a relatively longer period of time for the urinary NGAL level to increase compared with the urinary L-FABP level.

Another difference between urinary L-FABP and urinary NGAL for early detection of AKI in adult patients who undergo cardiac surgery relates to whether they are affected by preoperative comorbidities or not. Urinary NGAL is readily influenced by preoperative comorbidities such as diabetes, hypertension, hyperlipidemia and cardiovascular disease. Wagener et al reported that because of increased rates of preoperative comorbidities in adults, the ability of urinary NGAL to predict AKI after cardiac surgery in adults was inferior to that in children.[37] In the present study and in the Wagener et al study,[37] many patients had an increase in urinary NGAL level after cardiac surgery, and only the degree of the change differed in patients with or without AKI compared with the pediatric population who do not have preoperative comorbidities. In contrast, urinary L-FABP is a well-established biomarker both in children[15] and in adults.[27]

In the present study we did not measure serum L-FABP in either the AKI group or in the non-AKI group. Previous studies in patients with chronic kidney disease, acute renal failure and sepsis have shown that serum L-FABP level does not influence the urinary level.[38,39] Thus, we did not measure serum L-FABP level in the present study.

Some findings in the present study conflicted with previous studies. Wijeysundera et al proposed that preoperative eGFR <60 ml/min was an independent predictor that was significantly associated with the onset of AKI, and lower preoperative eGFR was a stronger predictive factor for the onset of AKI.[40] In the present study, the preoperative eGFR level, which was estimated using the equation proposed by the Japanese Society of Nephrology {eGFR ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$)=$194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female)},[41] was significantly lower in the AKI group ($57.4 \pm 2.6\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) than in the non-AKI group ($71.8 \pm 3.9\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$; P=0.008). Preoperative eGFR, however, was not an independent predictor on multiple logistic regression analysis. Furthermore, although the operation time was longer in the AKI group than in the non-AKI group, the operation time was not a risk factor for the onset of AKI. Because patients who were scheduled to undergo various surgical procedures were recruited in the present study, we speculate that the operation time directly reflected the ischemic period during which renal blood flow was reduced. In order to clarify these points, further research in a large-scale multicenter trial is needed.

Conclusions

In adult patients, the presence of tubular damage and the deterioration of tubular structure were risk factors for the onset of AKI, and urinary L-FABP was a useful biomarker for early detection of AKI and was a good early predictor for the onset of AKI. Further investigation is required to establish the optimal timing of urinary L-FABP measurement and the optimal cut-off points for clinical use of urinary L-FABP in the cardiac surgical department.

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