INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Comparison of the Renoprotective Effect of Febuxostat for the Treatment of Hyperuricemia between Patients with and without Type 2 Diabetes Mellitus: A Retrospective Observational Study

Hiroyuki Ito[1], Shinichi Antoku[1], Mariko Abe[1], Takashi Omoto[1], Masahiro Shinozaki[1], Shinya Nishio[1], Mizuo Mifune[1], Michiko Togane[1], Masaya Nakata[2] and Tatsuya Yamashita[2]

Abstract

Objective The effects of febuxostat therapy on hyperuricemia in patients with and without type 2 diabetes were compared in this retrospective observational study after pair-matching using the propensity scores.

Methods In total, 160 patients with hyperuricemia were studied as the treated set, and the 155 subjects in whom the administration of febuxostat was not discontinued during the observation period were investigated in the full analysis. The study subjects were divided into two groups based on the style of initiation of febuxostat: initial and switching therapy from allopurinol administration.

Results The reduction in the serum uric acid (sUA) levels at six months after the initiation of febuxostat administration did not significantly differ between the patients with and without diabetes in both the initial (206 ±114 and 226±113 μmol/L in patients with and without diabetes, respectively) and switching (154±91 and 129±90 μmol/L in patients with and without diabetes, respectively) therapy groups. The eGFR values were significantly increased compared to the baseline levels only in the patients without diabetes. The changes in the eGFR values were significantly associated with the presence of diabetes and sUA at baseline in a multivariate analysis. The frequency of adverse events was not significantly different between the patients with and without diabetes.

Conclusion Although febuxostat exerted a similar sUA-lowering effect against hyperuricemia in patients with type 2 diabetes compared to those without, the renoprotective effect was attenuated in those with diabetes compared to nondiabetic subjects.

Key words: allopurinol, febuxostat, xanthine oxidase inhibitor, hyperuricemia, renoprotection, type 2 diabetes mellitus

(Intern Med 55: 3247-3256, 2016)
(DOI: 10.2169/internalmedicine.55.6791)

Introduction

Hyperuricemia is well known to cause renal dysfunction (1-3) as well as gout (4, 5). Recently, hyperuricemia was reported to also be a risk factor for conditions involving atherosclerosis, such as coronary heart disease and cerebrovascular disease (6-8), although this issue remains controversial. Renal impairment and atherosclerotic diseases commonly occur in patients with type 2 diabetes mellitus, in a condition known as diabetic angiopathy. In addition, we previously demonstrated that coronary heart disease and the progression of renal impairment are frequently observed in Japanese patients with both type 2 diabetes and hyperuricemia (9).

The administration of allopurinol, a xanthine oxidase inhibitor, has been reported to ameliorate the progression of renal impairment (10, 11) and the risk of cardiovascular events (11, 12) in patients with hyperuricemia. Febuxostat is a novel selective xanthine oxidase inhibitor. In addition to

[1]Department of Diabetes, Metabolism and Kidney Disease, Edogawa Hospital, Japan and [2]Department of Cardiology, Edogawa Hospital, Japan
Received for publication November 4, 2015; Accepted for publication April 7, 2016
Correspondence to Dr. Hiroyuki Ito, ito@edogawa.or.jp

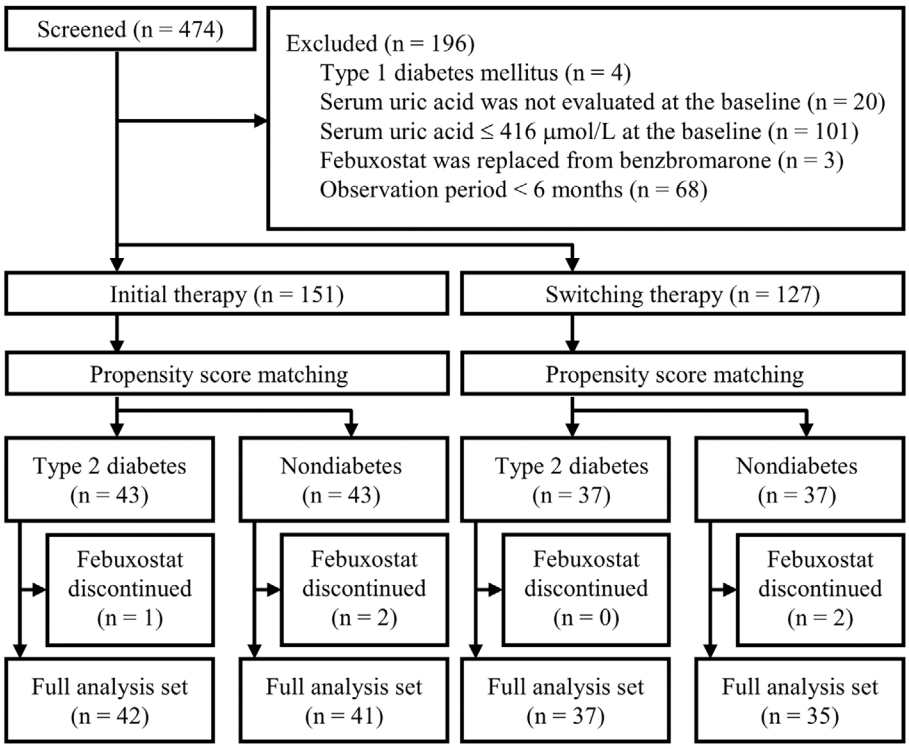

Figure 1. The flowchart of the patient selection. The safety of febuxostat was analyzed in the treated set (n=160), and the effectiveness was investigated in the full analysis set (n=155).

the findings of preclinical studies (13-19), it had been reported that the rate of achievement of the treatment goal for the serum uric acid (sUA) level is significantly higher in subjects receiving febuxostat administration than in those receiving treatment with allopurinol among individuals with gout (20, 21) and hyperuricemic patients with a history of cardiac surgery (22) in real clinical practice. Furthermore, it was recently demonstrated that the renal function is preserved following a reduction in the sUA level after febuxostat therapy in hyperuricemic gout subjects (23). Although sUA levels were reduced in both hyperuricemic patients with and without diabetes (24) based on the results of a post-hoc analysis of a large dataset (21), no previous studies have compared the renoprotective effects in these groups.

We therefore examined the effects of febuxostat for the treatment of hyperuricemia in patients with and without type 2 diabetes in a retrospective observational study.

Materials and Methods

Subjects

A flowchart of the patient selection is shown in Fig. 1. A total of 474 patients with hyperuricemia who received 10-60 mg of febuxostat (Feburic®; Teijin Pharma, Tokyo, Japan) once daily at the Department of Diabetes, Metabolism and Kidney Disease or Department of Cardiology at our hospital between August 2011 and June 2014 were eligible for this study. The patients with type 1 diabetes, those in whom the sUA level was not evaluated or was ≤416 μmol/L at the initiation of febuxostat treatment, those in whom the administration of febuxostat was started after switching from benzbromarone, and those with an observation period of less than 6 months were excluded from the analysis.

The subjects were divided into two groups based on the style of initiation of febuxostat: patients in whom febuxostat was started as the first-line agent (initial therapy group, n= 151, 64 diabetic and 87 nondiabetic patients) and those who were switched from allopurinol (switching therapy group, n=127, 66 diabetic and 61 nondiabetic patients). To guarantee the validity of this retrospective analysis, a propensity score was applied for the pair-matching between the subjects with and without diabetes. The propensity score was calculated using a logistic analysis, including the age, gender, sUA, serum creatinine concentration, and estimated glomerular filtration rate (eGFR) at the initiation of febuxostat administration. Based on the scores of each subject, the two patients whose scores fell within 0.03 of each other were selected as a pair to compare the effect of febuxostat between the patients with and without diabetes. In total, 86 patients in the initial therapy group and 74 in the switching therapy group were studied as the treated set to analyze the safety of febuxostat. Furthermore, 83 and 72 subjects in the initial therapy and switching groups, respectively, in whom the administration of febuxostat was not discontinued during the observation period of six months were investigated as the full analysis set to assess the effectiveness of febuxostat in each treatment group.

The starting dose of febuxostat was 10 mg once daily in the initial therapy group and 20 mg once daily in the

switching group, to avoid the onset of gout attacks induced by a rapid improvement in the sUA level. The dose of febuxostat used in each subject was determined by the attending physician at each hospital visit. The clinical parameters and adverse events (AEs) after the initiation of febuxostat were examined retrospectively based on the medical records of the patients.

Confounding factors

The eGFR was calculated using the formula reported by Matsuo et al. (25). This equation, developed by the MDRD study group (26), was created for use in Japanese individuals and is recommended by the Japanese Society of Nephrology:

eGFR (mL/min/1.73 m^2)=194×$Scr^{-1.094}$×$Age^{-0.287}$(×0.739 if female)

The stage of albuminuria was classified based on the urinary albumin-to-creatinine ratio (ACR) as A1 (ACR <30 mg/g/cr), A2 (30 mg/g/cr ≤ ACR <300 mg/g/cr) or A3 (300 mg/g/cr ≤ ACR) (27). Obese individuals were defined as those with a body mass index (BMI) of ≥25 kg/m^2. Hypertension was defined as either or both a systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg. Participants currently using antihypertensive medications were also classified as being positive for hypertension. Hyper-LDL cholesterolemia was defined as a serum concentration of LDL-cholesterol of ≥3.62 mmol/L or the current use of statins or ezetimibe. A drinker was defined as drinking >20 g ethanol equivalents/day.

Diabetic retinopathy was graded as simple, preproliferative, or proliferative retinopathy based on the results of a funduscopic examination performed by expert ophthalmologists. Diabetic neuropathy was diagnosed by the presence of two or more components among clinical symptoms (bilateral spontaneous pain, hypoesthesia, or paraesthesia of the legs), the absence of ankle tendon reflexes, and decreased vibration sensations using a C128 tuning fork.

Cerebrovascular disease was diagnosed by the physicians as a history of an ischemic stroke using brain computed tomography or magnetic resonance imaging. Only the patients with symptoms were classified as having cerebrovascular disease, and cases of silent brain infarction, transient ischemic attack, and a brain hemorrhage were excluded from this study. Coronary heart disease was diagnosed based on a previous history of myocardial infarction, angina pectoris, electrocardiogram abnormalities suggesting myocardial ischemia, or interventions after a coronary angiographic examination. Peripheral arterial disease was diagnosed by the absence of a pulse in the legs, along with ischemic symptoms, obstructive findings on an ultrasonographic or angiographic examination of the lower extremities, or an ankle-brachial pressure index (ABI) <0.9.

If any clinical data, including the serum uric acid level, were missing, the appropriate value obtained on the previous visit was used in accordance with the last observation carried forward (LOCF) method.

Ethics statement

The study was conducted in accordance with the principles expressed in the 2008 Declaration of Helsinki. The Ethics Committee of Edogawa Hospital approved the study protocol and waived the need for written informed consent because the data were analyzed anonymously for this retrospective analysis based on information stored in the hospital.

Statistical analyses

All of the data are presented as the mean ± SD. The Wilcoxon rank sum test and the χ^2 test were used for between-group comparisons of continuous and categorical variables. The repeated-measure analysis of variance was employed to determine the presence of differences in the data for BMI, blood pressure, the serum transaminase levels indicating the liver function, lipids, sUA, HbA1c, and eGFR at the end of the study period compared with the baseline values. A least-squares model was used to evaluate the associations between the changes in the sUA levels or eGFR values and the clinical background factors of the patients. A multivariate analysis was performed using only the factors that demonstrated a significant association with the changes in the sUA levels or eGFR values in the univariate analysis as an independent variable. Differences with a p value of <0.05 (two-tailed) were considered to be statistically significant. The statistical software package JMP version 8.0.1 (SAS Institute, Cary, NC, USA) was used to perform all analyses.

Results

Baseline clinical characteristics of the full analysis set

The mean sUA and eGFR values for all subjects were 517±77 μmol/L (range: 422-827 μmol/L) and 37.5±12.0 mL/min/1.73 m^2 (range: 16.2-59.7 mL/min/1.73 m^2), respectively. The baseline clinical characteristics of the subjects before the matching and the full analysis set are shown in Table 1. After the matching, a drinking habit was significantly more frequent among the patients without diabetes in the initial therapy group than among those in the switching therapy group. The frequency of obesity was higher among the patients in the switching therapy group than among those in the initial therapy, whereas coronary heart disease was more frequent among the patients in the initial therapy group. The eGFR values and sUA levels did not differ markedly between the patients with and without diabetes. The daily dose of allopurinol prior to switching to febuxostat was 114±59 and 126±59 mg in the patients with and without diabetes, respectively.

Changes in the clinical parameters during the observation period

The changes in the sUA levels are shown in Fig. 2. The sUA levels significantly improved after the initiation of fe-

Table 1. **The Baseline Clinical Characteristics of the Subjects before Matching and the Full Analysis Set.**

	Initial therapy						Switching therapy					
	Before matching			Full analysis set			Before matching			Full analysis set		
	Diabetes (n = 64)	Non-diabetes (n = 87)	p	Diabetes (n = 42)	Non-diabetes (n = 41)	p	Diabetes (n = 66)	Non-diabetes (n = 61)	p	Diabetes (n = 37)	Non-diabetes (n = 35)	p
Male (%)	83	69	0.049	79	66	0.19	80	75	0.51	73	80	0.48
Age (years)	69 ± 13	69 ± 14	0.79	71 ± 11	73 ± 14	0.33	66 ± 13	66 ± 13	0.70	68 ± 13	68 ± 12#	0.50
Duration of diabetes (years)	14 ± 12	-	-	14 ± 11	-	-	15 ± 13	-	-	14 ± 13	-	-
Drinker (%)	36	43	0.38	33	33	0.94	38	66#	<0.01	42	64##	0.07
Current smoker (%)	13	11	0.68	13	8	0.48	16	16	0.92	25	13	0.23
Body mass index (kg/m^2)	25.0 ± 4.7	23.8 ± 3.7	0.20	25.1 ± 470	23.9 ± 3.6	0.30	26.8 ± 5.5#	26.0 ± 4.4##	0.48	26.0 ± 4.0	26.1 ± 5.0#	0.79
Obesity (%)	37	28	0.25	34	29	0.60	57#	50#	0.44	57#	48	0.48
Hypertension (%)	95	95	0.98	100	95	0.05	91	84#	0.21	89	94	0.43
RAS inhibitor use* (%)	75	79	0.53	83	76	0.38	65	64#	0.89	65	83	0.08
Calcium channel blocker use (%)	53	38	0.06	60	34	0.02	59	43	0.06	54	43	0.34
Hyper-LDL cholesterolemia (%)	69	67	0.79	74	68	0.58	71	67	0.63	78	71	0.50
Diabetic retinopathy** (%)	61	-	-	65	-	-	62	-	-	74	-	-
Diabetic neuropathy (%)	67	-	-	68	-	-	77	-	-	72	-	-
Cerebrovascular disease (%)	19	15	0.54	19	15	0.59	18	15	0.60	19	20	0.91
Coronary heart disease (%)	44	45	0.90	48	44	0.73	26#	21##	0.56	27	20#	0.48
Peripheral arterial disease (%)	8	3	0.24	12	5	0.24	12	5	0.14	11	9	0.75
Systolic blood pressure (mmHg)	133 ± 25	130 ± 18	0.71	132 ± 23	128 ± 16	0.94	131 ± 17	126 ± 17	0.21	134 ± 18	122 ± 17	0.02
Diastolic blood pressure (mmHg)	74 ± 19	74 ± 15	0.57	70 ± 17	72 ± 13	0.31	75 ± 16	74 ± 13	0.95	77 ± 16#	74 ± 14	0.50
Aspartate transaminase (IU/L)	26 ± 17	26 ± 13	0.27	24 ± 16	26 ± 12	0.17	28 ± 19	25 ± 10	0.85	28 ± 19	26 ± 10	0.71
Alanine transaminase (IU/L)	23 ± 22	21 ± 13	0.88	19 ± 11	19 ± 14	0.90	25 ± 25	23 ± 13	0.49	21 ± 10	24 ± 15	0.45
LDL cholesterol (mmol/L)	2.53 ± 0.89	2.61 ± 1.03	0.72	2.48 ± 0.85	2.61 ± 1.03	0.72	2.55 ± 0.85	2.74 ± 0.85	0.14	2.39 ± 0.76	2.60 ± 0.77	0.31
HDL cholesterol (mmol/L)	1.10 ± 0.32	1.28 ± 0.44	0.02	1.06 ± 0.31	1.24 ± 0.48	0.11	1.10 ± 0.30	1.24 ± 0.33	<0.01	1.07 ± 0.29	1.22 ± 0.35	0.04
Serum creatinine (μmol/L)	145 ± 79	114 ± 53	<0.01	140 ± 52	126 ± 37	0.34	151 ± 80	148 ± 108	0.27	132 ± 41	140 ± 48	0.39
Estimated GFR (mL/min/1.73 m^2)	40.4 ± 18.3	48.8 ± 20.8	0.01	36.8 ± 12.3	38.1 ± 12.0	0.59	39.7 ± 20.0	43.8 ± 22.8	0.35	38.0 ± 11.7	37.2 ± 12.5	0.60
Albuminuria*** (%)	65	-	-	69	-	-	81	-	-	76	-	-
HbA1c (%)	6.8 ± 0.85	-	-	6.7 ± 1.2	-	-	7.2 ± 1.6	-	-	7.1 ± 1.3	-	-
Serum uric acid (μmol/L)	543 ± 98	529± 74	0.54	535 ± 99	541 ± 75	0.31	486 ± 55##	489 ± 59##	0.98	499 ± 56	487 ± 52##	0.25

RAS: renin-angiotensin system

* RAS inhibitors include angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

** Diabetic retinopathy includes simple, preproliferative, and proliferative retinopathy.

*** Albuminuria includes albuminuria stages A2 and A3.

# $p < 0.05$ and ## $p < 0.01$ vs. the corresponding value in the initial therapy group.

buxostat treatment in both the patients receiving initial febuxostat and the switching therapy group. The reduction in the sUA levels at six months after the initiation of febuxostat administration was not significantly different between the patients with and without diabetes in both the initial (206±114 and 226±113 μmol/L in patients with and

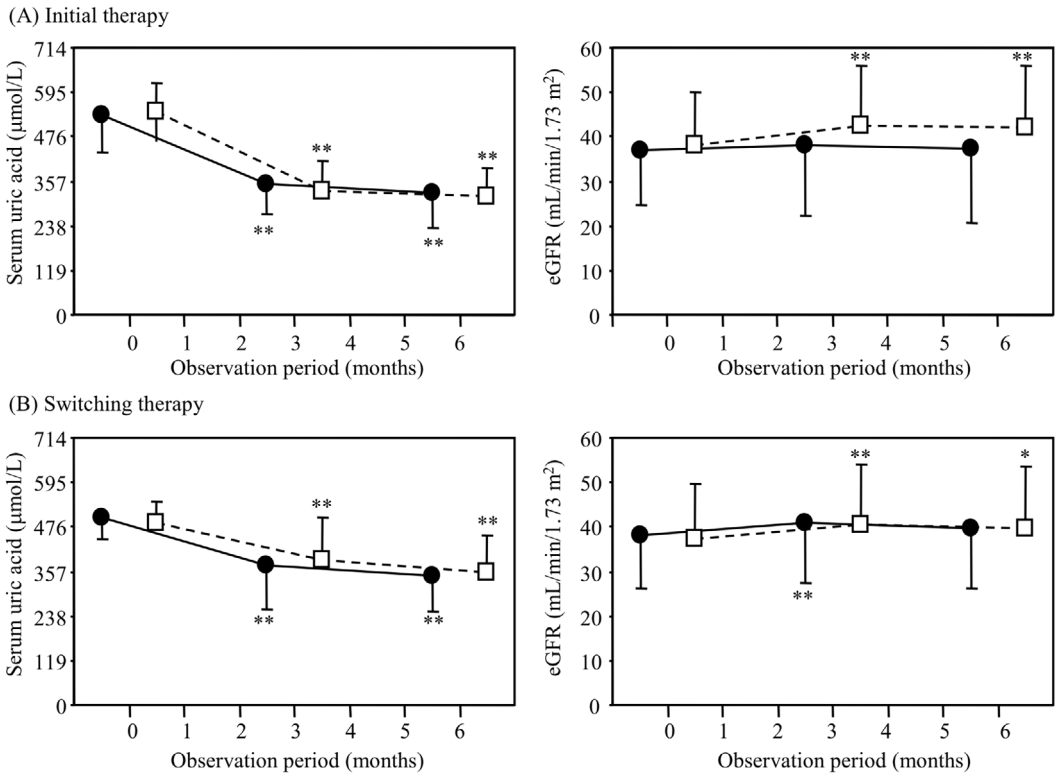

Figure 2. **Changes in the serum uric acid and eGFR levels in the (A) initial therapy group (n=83) and the (B) switching therapy group (n=72). The closed circles indicate the serum uric acid or eGFR levels in the patients with type 2 diabetes, and the open squares indicate those values in the patients without diabetes. *p<0.05 and **p<0.01 vs. the baseline (0 month) value.**

Table 2. **The Changes in the Clinical Parameters of the Full Set Analysis at Six Months after the Initiation of Febuxostat.**

	Initial therapy			Switching therapy		
	Diabetes (n = 42)	Non-diabetes (n = 41)	p	Diabetes (n = 37)	Non-diabetes (n = 35)	p
Body mass index (kg/m^2)	0.0 ± 2.1	-0.0 ± 0.9	0.24	0.0 ± 1.2	-0.1 ± 0.8	0.86
Systolic blood pressure (mmHg)	-2 ± 21	4 ± 17	0.62	2 ± 16	5 ± 14	0.49
Diastolic blood pressure (mmHg)	-1 ± 15	1 ± 13	0.77	1 ± 13	1 ± 9	0.54
Aspartate transaminase (IU/L)	-2 ± 13	-1 ± 8	0.95	-2 ± 13	-5 ± 9	0.14
Alanine transaminase (IU/L)	-1 ± 8	0 ± 8	0.57	-2 ± 8	-6 ± 12##	0.40
LDL cholesterol (mmol/L)	-0.10 ± 0.66	-2.02 ± 0.58#	0.76	-0.00 ± 27	-0.09 ± 24	0.41
HDL cholesterol (mmol/L)	0.10 ± 0.45	0.03 ± 0.27#	0.39	0.09 ± 0.15##	0.01 ± 0.17	0.14
Serum creatinine (μmol/L)	13 ± 58	-11±25##	0.01	-2 ± 20	-6 ± 23	0.48
Estimated GFR (mL/min/1.73 m^2)	0.4± 9.0	4.1 ± 7.7##	0.02	1.6 ± 6.1	2.8 ± 7.0#	0.56
Albuminuria* (%)	-4	-	-	-8	-	-
HbA1c (%)	-0.1 ± 0.9	-	-	-0.1 ± 1.1	-	-
Serum uric acid (μmol/L)	-206 ± 114	-226 ± 113##	0.64	-154 ± 91##	-129 ± 90##	0.24
Proportion of serum uric acid ≤ 357 μmol/L (%)	67##	71##	0.69	62##	51##	0.36
Proportion of serum uric acid ≤ 416 μmol/L (%)	86##	95##	0.14	78##	69##	0.35

* Diabetic nephropathy includes albuminuria stages A2 and A3.
# p < 0.05 and ## p < 0.01 vs. the corresponding value at baseline.

without diabetes, respectively) and switching (154±91 and 129±90 μmol/L in patients with and without diabetes, respectively) therapy groups (Table 2). The proportion of patients who achieved a sUA level of ≤357 μmol/L at the end of the observation period was not significantly different between the subjects with and without diabetes in both the initial (67% and 71% in patients with and without diabetes, respectively) and switching (62% and 51% in patients with and without diabetes, respectively) therapy groups (Table 2). The proportions of patients who achieved a sUA level of ≤416 μmol/L were not also significantly different between therapy groups (Table 2). The daily dose of febuxostat at the end of the observation period was 16±7 and 14±5 mg in the diabetic and nondiabetic patients in the initial therapy group, and 24±10 and 22±8 mg in the diabetic and nondiabetic patients in the switching therapy group, respectively.

Table 3. The Relationships between the Changes in the Serum Uric Acid Level at Six Months after the Initiation of Febuxostat and the Clinical Parameters at Baseline in the Full Analysis Set.

	Univariate		Multivariate	
	Regression coefficient	p	Regression coefficient	p
Diabetes (%)	-0.10	0.99		
Initial therapy (%)	-36.90	< 0.01	-17.87	0.03
Male (%)	14.17	0.16		
Age (years)	-1.38	0.047	-1.01	0.11
Drinker (%)	20.86	0.03	10.32	0.20
Current smoker (%)	11.74	0.37		
Body mass index (kg/m^2)	1.63	0.45		
Obesity (%)	2.86	0.76		
Hypertension (%)	6.69	0.74		
RAS inhibitor use (%)	23.28	0.03	9.27	0.31
Calcium channel blocker use (%)	1.26	0.86		
Hyper-LDL cholesterolemia (%)	9.17	0.36		
Cerebrovascular disease (%)	-1.46	0.90		
Coronary heart disease (%)	2.34	0.80		
Peripheral arterial disease (%)	15.85	0.30		
Systolic blood pressure (mmHg)	-0.12	0.80		
Diastolic blood pressure (mmHg)	0.34	0.59		
Aspartate transaminase (IU/L)	-0.13	0.84		
Alanine transaminase (IU/L)	0.63	0.37		
LDL cholesterol (mmol/L)	-14.83	0.16		
HDL cholesterol (mmol/L)	-15.81	0.52		
Serum creatinine (μmol/L)	-0.01	0.98		
Estimated GFR (mL/min/1.73 m^2)	0.73	0.32		
Serum uric acid (μmol/L)	-0.79	< 0.01	-0.72	< 0.01

RAS: renin-angiotensin system

The changes in the clinical parameters in the full analysis set at six months after the initiation of febuxostat therapy are shown in Table 2. The changes in the values for BMI, blood pressure, serum transaminases, LDL-cholesterol, and HDL-cholesterol did not differ markedly between the subjects with and without diabetes. Although the eGFR levels were significantly increased compared to the baseline values among the patients without diabetes in both the initial (4.1±7.7 mL/min/1.73 m^2) and switching (2.8±7.0 mL/min/1.73 m^2) therapy groups, this parameter did not differ markedly compared with baseline among those with diabetes (Table 2 and Fig. 2). Furthermore, the proportion of patients with albuminuria (an ACR ≥30 mg/g/cr) did not change markedly from baseline among the patients with diabetes (Table 2).

Table 3 shows the relationships between the change in the sUA levels at six months after the initiation of febuxostat therapy and the clinical parameters at baseline in the full analysis set. The decrease observed in the sUA level of the initial therapy group was larger than that in the switching therapy group. The reduction in the sUA was larger when the initial sUA level was high, although the change in the sUA was not associated with the presence of diabetes, drinking habit, serum creatinine level, or eGFR value.

According to our multivariate analysis, the increase in the eGFR value at six months was greater in the patients without diabetes and with a high baseline sUA value than in those without diabetes and with a relatively low baseline sUA value; however, this parameter was not related to the style of initiation of febuxostat or the serum creatinine or eGFR levels (Table 4). Furthermore, the change in the eGFR value was significantly greater in the patients who achieved a sUA level of ≤357 μmol/L at the end of the observation period than in those who did not (1.9±7.1 mL/min/1.73 m^2 vs. -0.7±8.7 mL/min/1.73 m^2, p=0.04 in the subjects with diabetes and 5.7±7.4 mL/min/1.73 m^2 vs. -0.1±5.9 mL/min/1.73 m^2, p <0.01 in the subjects without diabetes). The change in the eGFR value also showed a significantly negative association with the change in the sUA during the observation period (Fig. 3).

Adverse events during the observation period

The administration of febuxostat was discontinued in 5 patients (3.1%), who were subsequently excluded from the full analysis set, in the treated set (n=160) during the observation period (Fig. 1) due to vertigo (n=1), skin eruptions (n =1), hyperkalemia (n=1), the self-judgment of the patient (n =1), and unknown reasons (n=1). The frequency of the AEs recorded in the treated set was not significantly different between the patients with (11 cases among 80 patients; 13.8%) and without (16 cases among 80 patients; 20.0%) diabetes. AEs observed in more than 2% of the treated set included congestive heart failure (n=6; 3.8%) and vertigo (n=6, 3.8%). No gout attacks were reported during the observation period.

Discussion

In the present study, the lowering effect of febuxostat on the sUA levels was not significantly different between the patients with and without diabetes in both the initial and

Table 4. The Relationships between the Changes in the eGFR Level at Six Months after the Initiation of Febuxostat and the Clinical Parameters at Baseline and the Changes in the Serum Uric Acid Level at the End of Observation in the Full Analysis Set.

	Univariate		Multivariate	
	Regression coefficient	p	Regression coefficient	p
Diabetes (%)	-1.246	0.04	-1.248	0.03
Initial therapy (%)	0.026	0.97		
Male (%)	0.310	0.66		
Age (years)	-0.041	0.41		
Drinker (%)	0.928	0.14		
Current smoker (%)	-1.687	0.06		
Body mass index (kg/m^2)	0.276	0.08		
Obesity (%)	1.230	0.08		
Hypertension (%)	0.356	0.80		
RAS inhibitor use (%)	1.865	0.42		
Calcium channel blocker use (%)	0.464	0.46		
Hyper-LDL cholesterolemia (%)	-0.341	0.62		
Cerebrovascular disease (%)	-0.684	0.39		
Coronary heart disease (%)	0.007	0.99		
Peripheral arterial disease (%)	-0.458	0.67		
Systolic blood pressure (mmHg)	-0.029	0.40		
Diastolic blood pressure (mmHg)	0.024	0.58		
Aspartate transaminase (IU/L)	0.049	0.29		
Alanine transaminase (IU/L)	0.033	0.50		
LDL cholesterol (mmol/L)	0.271	0.71		
HDL cholesterol (mg/dL)	2.737	0.11		
Serum creatinine (μmol/L)	-0.007	0.59		
Estimated GFR (mL/min/1.73 m^2)	0.028	0.59		
Serum uric acid (μmol/L)	0.024	< 0.01	0.024	< 0.01

RAS: renin-angiotensin system

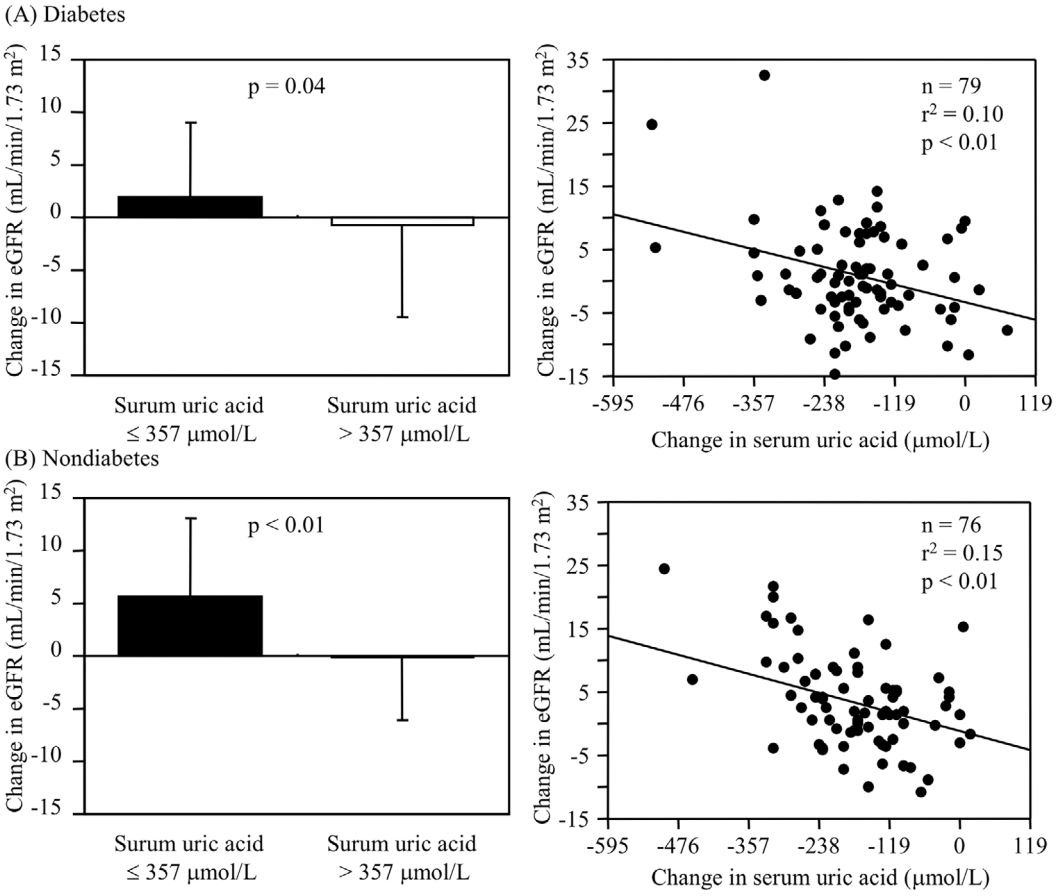

Figure 3. Comparisons of the changes in the eGFR between the subjects who achieved a serum uric acid level ≤357 μmol/L and those who did not at the end of the observation period, as well as the relationships between the changes in the eGFR values and serum uric acid levels among the patients (A) with and (B) without diabetes.

switching therapy groups. Approximately 50-70% of the subjects receiving febuxostat treatment achieved a sUA level of ≤357 μmol/L at the end of the observation period in all of the groups in this study. In a phase III trial performed in Japanese patients with hyperuricemia, 45.7% and 91.2% of the subjects achieved a sUA level of ≤357 μmol/L after 8 weeks of treatment with febuxostat at a dose of 20 mg (n=35) and 40 mg (n=34) once daily, respectively (14). Furthermore, in another phase III trial in Japan, 82% of the hyperuricemic patients achieved a sUA level ≤ of 357 μmol/L after 8 weeks of treatment with febuxostat at a dose of 40 mg (n=122) once daily, while only 70% of the subjects receiving 200 mg of allopurinol twice daily achieved a sUA levels of ≤357 μmol/L (13). In the current study, the daily dose of febuxostat remained around 20 mg at the end of the observation period in each group. A sUA level of ≤357 μmol/L is recommended in patients with gouty arthritis or gouty tophi, according to the guidelines published by the Japanese Society of Gout and Nucleic Acid Metabolism (28). However, the target level of sUA for preventing the progression of renal impairment is still unknown. We believe that the proportion of subjects who achieved a sUA level of ≤357 μmol/L and the daily dose of febuxostat in the present study were likely lower than in previous preclinical trials because the dose of febuxostat used in individual subjects was determined by the attending physician (13-19). This lower dose of febuxostat might have been associated with the relatively low frequency of AEs during the observation period in the current study.

Recently, Becker et al. investigated the efficacy and safety of febuxostat and allopurinol at commonly prescribed doses in patients with diabetes and gout (19) based on a post-hoc analysis in the CONFIRMS trial (24). In that study, more subjects achieved a sUA level <357 μmol/L in the group that received febuxostat at a dose of 80 mg than in the group that received a dose of 40 mg or allopurinol (200 mg or 300 mg daily) among both the diabetic and nondiabetic patients, although the changes in the eGFR levels were not determined. The present study is the first report to investigate the renoprotective effects of febuxostat in patients with diabetes. Consequently, the eGFR values significantly improved after febuxostat therapy among the nondiabetic subjects in both the initial and switching therapy groups in the present study, whereas the eGFR values did not differ markedly among the patients with diabetes. The major mechanism of renal injury by hyperuricemia is tubulointerstitial nephritis secondary to the deposition of uric acid. Difficulty in the management of hypertension (29) and the accumulation of risk factors for atherosclerosis (30) are commonly found in patients with diabetes with chronic kidney disease in addition to hyperglycemia, which is a primary cause of diabetic nephropathy.

In the present study, calcium channel blockers were used significantly more frequently in the patients with diabetes than in those without diabetes in the initial therapy group (Table 1). The level of systolic blood pressure was significantly higher in the patients with diabetes than in those without diabetes. In addition, the switching therapy group had significantly lower serum HDL-cholesterol concentrations. The concomitance of these factors exacerbating renal dysfunction might be one of the reasons for the differences in the renoprotective effect between the patients without and with diabetes. Preventing the progression of renal dysfunction is generally difficult in patients with overt nephropathy. Because the eGFR value was reduced at baseline in the current study, the impact of febuxostat on the renal function may have been attenuated in the patients with diabetes. Of note, we did not observe any obvious renoprotective effect in diabetic patients with normal renal function.

To our knowledge, no previous reports have investigated the effects after switching from allopurinol to febuxostat in patients with diabetes mellitus. Based on a direct comparison between febuxostat and allopurinol administration in double-blind phase III trials, treatment with febuxostat at a daily dose of 80 or 120 mg is more effective than allopurinol at a daily dose of 300 mg in lowering the sUA level (15), and the sUA-lowering efficacy of febuxostat at a dose of 80 mg exceeds that of febuxostat at a dose of 40 mg as well as allopurinol at a dose of 200 or 300 mg (24). Sezai et al. also reported that the use of febuxostat up to a dose of 60 mg daily induces a superior sUA-lowering effect compared to allopurinol at a dose of up to 300 mg in hyperuricemic patients following cardiac surgery (22). In the present study, a renoprotective effect was also considered to exist in the switching therapy group, because the sUA was reduced after the replacement of allopurinol with febuxostat. In their study, Hatoum et al. demonstrated that 48.3% of hyperuricemic patients who were switched to febuxostat (48.4±15.8 mg/day) after failing to reach a sUA level of <357 μmol/L with allopurinol (184.9±96.7 mg/day) achieved a sUA level of <357 μmol/L within 6 months of switching (20). In the present study, the reduction in the sUA levels obtained with a relatively small daily dose of febuxostat was also superior in both the patients with and without diabetes switched from allopurinol, with a greater than 50% rate of achievement of a sUA level of ≤357 μmol/L. Therefore, switching to febuxostat is also considered to be effective in diabetic patients in whom the sUA level does not reach the target value with allopurinol treatment.

In the present study, the change in the eGFR value was significantly associated with not only the achievement of a sUA level of ≤357 μmol/L but also the change in the sUA level throughout the observation period. Therefore, febuxostat administration is expected to have a renoprotective effect even if the sUA level does not reach the treatment goal. Furthermore, a better result with respect to preservation of the renal function may be obtained by increasing the dose of febuxostat, as the sUA level has been reported to decrease in a dose-dependent manner following a change in febuxostat treatment from 20 mg up to 60 mg daily in phase II clinical trials performed in Japan (13, 16). Moreover, the clinical renoprotective effects of treatment with allopurinol

for hyperuricemia have been previously reported in patients with chronic kidney disease (10, 11) and type 1 diabetes (31), and febuxostat treatment prevents the progression of renal dysfunction, depending on the degree of reduction in the sUA level, in patients with gout (23). With respect to the findings from animal studies, the reduction in the sUA level obtained with allopurinol administration attenuated the TGF-β1-induced profibrogenic progression of nephropathy in KK-A^{y}/Ta mice, an animal model of type 2 diabetes (32). Furthermore, febuxostat has been shown to ameliorate renal injury by relieving the inflammatory and oxidative stress (33) and reducing the endothelial dysfunction (34) in a rat model of streptozotocin-induced diabetes.

In the current study, the frequency of AEs did not differ markedly between the patients with and without diabetes. However, the incidence of AEs appeared to be lower in the present study than in preclinical trials (13-19, 23) and real clinical data (21, 24). Notably, however, some AEs may have been missed, as the present analysis was performed based on the medical records. Because this drug was only recently released and evidence is therefore sparse, physicians should practice caution when administering febuxostat in patients with type 2 diabetes and hyperuricemia, although only a small number of individuals discontinued febuxostat treatment during the observation period in the present study.

Several limitations associated with the present study warrant mention. First, this study was a retrospective observational investigation of a rather small number of patients. Therefore, we must consider that the changes in the clinical parameters, such as the serum lipid concentrations and eGFR values, may have occurred incidentally due to the low statistical power of the study. Further investigations in a larger number of patients should therefore be performed to confirm our results. Second, the observation period was considered to be rather short with respect to evaluating the changes in the renal function. A preclinical trial performed in Japan showed that eGFR levels were preserved until 52 weeks in patients with hyperuricemia, including rates of diabetes of approximately 10% in all groups with normal, mild, and moderate/severe renal impairment (15). Third, the sUA-lowering effect of febuxostat was considered to be insufficiently evaluated in the present study, as the dose of febuxostat was determined by the attending physician as described above. Better control of the sUA level and renal function may have been obtained with a sufficient increase in the dose of febuxostat and a longer observation period.

Conclusion

Although the sUA-lowering effects achieved with the administration of febuxostat hyperuricemia were similar between patients with and without type 2 diabetes, the renoprotective effect observed in nondiabetic subjects was attenuated in those with diabetes.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank Tomoko Koyanagi in the secretarial section and Tomomi Daido of the medical division of Edogawa Hospital for their valuable help with data collection.

References

1. Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. Am J Kidney Dis **44**: 642-650, 2004.
2. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol **19**: 2407-2413, 2008.
3. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med **169**: 342-350, 2009.
4. Lin KC, Lin HY, Chou P. The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. J Rheumatol **27**: 1501-1515, 2000.
5. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum **51**: 321-325, 2004.
6. Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. Hypertension **36**: 1072-1078, 2000.
7. Kawai T, Ohishi M, Takeya Y, et al. Serum uric acid is an independent risk factor for cardiovascular disease and mortality in hypertensive patients. Hypertens Res **35**: 1087-1092, 2012.
8. Chuang SY, Chen JH, Yeh WT, Wu CC, Pan WH. Hyperuricemia and increased risk of ischemic heart disease in a large Chinese cohort. Int J Cardiol **154**: 316-321, 2012.
9. Ito H, Abe M, Mifune M, et al. Hyperuricemia is independently associated with coronary heart disease and renal dysfunction in patients with type 2 diabetes mellitus. PLoS One **6**: e27817, 2012.
10. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis **47**: 51-59, 2006.
11. Goicoechea M, de Vinuesa SG, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol **5**: 1388-1393, 2010.
12. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. Lancet **375**: 2161-2167, 2010.
13. Kamatani N, Fujimori S, Hada T, et al. Placebo-controlled double-blind dose-response study of the non-purine-selective xanthine oxidase inhibitor febuxostat (TMX-67) in patients with hyperuricemia (including gout patients) in Japan: late phase 2 clinical study. J Clin Rheumatol **17** (4 Suppl 2): S35-S43, 2011.
14. Kamatani N, Fujimori S, Hada T, et al. Placebo-controlled, double-blind study of the non-purine-selective xanthine oxidase inhibitor febuxostat (TMX-67) in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study. J Clin Rheumatol **17** (4 Suppl 2): S19-S26, 2011.
15. Kamatani N, Fujimori S, Hada T, et al. Multicenter, open-label study of long-term administration of febuxostat (TMX-67) in Japanese patients with hyperuricemia including gout. J Clin Rheumatol **17** (4 Suppl 2): S50-S56, 2011.
16. Kamatani N, Fujimori S, Hada T, et al. An allopurinol-controlled, multicenter, randomized, open-label, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia includ-

ing those with gout in Japan: phase 2 exploratory clinical study. J Clin Rheumatol **17** (4 Suppl 2): S44-S49, 2011.

17. Kamatani N, Fujimori S, Hada T, et al. An allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study. J Clin Rheumatol **17** (4 Suppl 2): S13-S18, 2011.

18. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med **353**: 2450-2461, 2005.

19. Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum **59**: 1540-1548, 2008.

20. Hatoum H, Khanna D, Lin SJ, Akhras KS, Shiozawa A, Khanna P. Achieving serum urate goal: a comparative effectiveness study between allopurinol and febuxostat. Postgrad Med **126**: 65-75, 2014.

21. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Res Ther **12**: R63, 2010.

22. Sezai A, Soma M, Nakata K, et al. Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients (NU-FLASH Trial). Circ J **77**: 2043-2049, 2013.

23. Whelton A, Macdonald PA, Zhao L, Hunt B, Gunawardhana L. Renal function in gout: long-term treatment effects of febuxostat. J Clin Rheumatol **17**: 7-13, 2011.

24. Becker MA, MacDonald PA, Hunt BJ, Jackson RL. Diabetes and gout: efficacy and safety of febuxostat and allopurinol. Diabetes Obes Metab **15**: 1049-1055, 2013.

25. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis **53**: 982-992, 2009.

26. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis **41**: 1-12, 2003.

27. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl **3**: 1-150, 2013.

28. Yamanaka H; Japanese Society of Gout and Nucleic Acid Metabolism. Japanese guideline for the management of hyperuricemia and gout: second edition. Nucleosides Nucleotides Nucleic Acids **30**: 1018-1029, 2011.

29. Ito H, Mifune M, Abe M, et al. Hypertension resistant to antihypertensive agents commonly occurs with the progression of diabetic nephropathy in Japanese patients with type 2 diabetes mellitus: a prospective observational study. BMC Nephrol **13**: 48, 2012.

30. Ito H, Antoku S, Furusho M, et al. The prevalence of the risk factors for atherosclerosis among type 2 diabetic patients is greater in the progressive stages of chronic kidney disease. Nephron Extra **3**: 66-72, 2013.

31. Maahs DM, Caramori L, Cherney DZ, et al. Uric acid lowering to prevent kidney function loss in diabetes: the preventing early renal function loss (PERL) allopurinol study. Curr Diab Rep **13**: 550-559, 2013.

32. Kim SM, Choi YW, Seok HY, et al. Reducing serum uric acid attenuates TGF-β1-induced profibrogenic progression in type 2 diabetic nephropathy. Nephron Exp Nephrol **121**: e109-e121, 2012.

33. Lee HJ, Jeong KH, Kim YG, et al. Febuxostat ameliorates diabetic renal injury in a streptozotocin-induced diabetic rat model. Am J Nephrol **40**: 56-63, 2014.

34. Hwang SJ, Lee KH, Jang HH, et al. Febuxostat contributes to improvement of endothelial dysfunction in an experimental model of streptozocin-induced diabetic rats. Int J Cardiol **171**: e110-e112, 2014.