Impact of serum uric acid on renal function and cardiovascular events in hypertensive patients treated with losartan

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High serum uric acid level (SUA) and chronic kidney disease (CKD) are risk factors for cardiovascular events (CVEs). However, their interactions as cardiovascular risk factors remain unknown. This subanalysis of the Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study included 7629 patients, in whom the serum creatinine level was measured at least twice. The study examined the impact of hyperuricemia (SUA $\geq$ 7 mg dl$^{-1}$) on CVE according to the level of renal dysfunction and whether early changes in SUA predicted future glomerular filtration rates (GFRs). The mean follow-up period was 3.1 years. The patients were divided into three groups according to the baseline estimated GFR (eGFR): groups A, B and C with eGFR $<$ 45, 45–59 and $\geq$ 60 ml min$^{-1}$ per 1.73 m$^2$, respectively. eGFR increased from 38.1 to 57.6, from 52.8 to 67.5 and from 74.7 to 80.7 ml min$^{-1}$ per 1.73 m$^2$ in groups A, B and C, respectively. In non-hyperuricemic patients, the CVE rate was 10.83, 4.98 and 4.21/1000 person-years in groups A, B and C, respectively, while in hyperuricemic patients, the corresponding values were 14.18, 17.02 and 5.93. Thus, hyperuricemia increased the risk of CVE only in group B (relative risk (RR) 3.43 (95% confidence interval (CI) 1.55 to 7.60); $P<0.002$). The final change in the eGFR was negatively correlated with the change in SUA from baseline to year 1 ($P<0.001$). CVEs were more frequent in those with a decrease in eGFR. Hyperuricemia may be a major determinant of increased cardiovascular risk in CKD stage 3A, and SUA may be involved in the progression of CKD.

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INTRODUCTION

Chronic kidney disease (CKD) is associated with an increase in cardiovascular morbidity and mortality. A reduced glomerular filtration rate (GFR) and albuminuria are independently associated with worse cardiovascular and renal outcomes in various populations. In the recently modified classification of CKD published in Kidney Disease: Improving Global Outcomes (KDOQI), stage 3 of CKD was subdivided into two stages (stage 3A and 3B with GFR 45–59 and 30–44 ml min$^{-1}$ per 1.73 m$^2$, respectively). It was shown that cardiovascular risk increases sharply when the estimated GFR (eGFR) falls below 45 ml min$^{-1}$ per 1.73 m$^2$ (ref. 5). Moreover, the new classification of CKD emphasizes that underlying diseases play an important role in cardio-renal outcomes in CKD.

Many studies suggest that an increased serum uric acid level (SUA) is associated with cardiovascular events (CVEs). Hyperuricemia is highly prevalent in patients with CKD. Thus, SUA may have a role in the increased cardiovascular mortality and morbidity associated with CKD. However, scant data exist on whether the impact of hyperuricemia on CVE differs according to the degree of renal dysfunction.

The issue of whether hyperuricemia is an independent risk factor for CKD remains controversial. A large number of cross-sectional studies have shown that hyperuricemia is independently and strongly associated with the prevalence of CKD. While prospective longitudinal studies also suggest that hyperuricemia may be an independent risk factor for CKD, its impact varies substantially among reports. In addition, there is little information regarding whether SUA influences future renal function in CKD patients.

The Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study was a nationwide, prospective, multicenter, observational study that examined the safety and
effectiveness of losartan-based antihypertensive therapy in 31,515 previously untreated hypertensive patients. All the patients were treated with losartan, which has been shown to lower SUA. In this subanalysis, we used data from 7629 patients whose SUA was measured at least twice and investigated whether the impact of SUA on CVE differs among three KDIGO categories of eGFR (<45, 45–59, >60 ml min⁻¹ per 1.73 m²), whether early changes in SUA during losartan treatment predict later GFR and whether shifts in GFR are associated with CVE.

**METHODS**

**Study design and setting**

The details of the J-HEALTH Study have been previously described. A total of 31,515 patients were screened between June 2000 and December 2001 in all of Japan's 47 prefectures at 3755 institutions by 4149 physicians. Among the study participants, 7629 patients in whom the serum creatinine level was measured at least twice were eligible for analysis.

Eligible patients were men or women >20 years of age with hypertension and who had not received any antihypertensive agents within the previous month. Before enrollment, each patient was informed of the purposes and methods of the study as well as the effects and possible risks of therapy, their right to withdraw from the study at any time and the measures taken to protect privacy. Each patient provided verbal informed consent. This trial was registered at https://center.umin.ac.jp as UMIN000006149.

The patients were initially treated with 25–50 mg of losartan once daily. If necessary, the dose could be increased up to 100 mg once daily. The addition of other antihypertensive agents was allowed 3 months after the start of losartan therapy. No restrictions were placed on the treatment of complications. Patients were followed for a maximum of 5 years, with a mean follow-up of 3.1 years.

Blood Pressure (BP) was measured by the methods typically used at each institution. After starting losartan therapy, BP was measured every 3 months during treatment. Standard laboratory tests were performed every 6 months. These were carried out in accordance with the routine methods used at each institution.

**Data sources/measurement**

The eGFR was calculated using the following equation for Japanese:

\[
eGFR = 194 \times \frac{1}{Cr^{1.006} \times \text{age}^{-0.20} \times (0.739 \text{for women})}
\]

CKD was defined as present when the eGFR was <60 ml min⁻¹ per 1.73 m². Urinary protein was examined by a dipstick method and classified as negative (−), +, ++, or +++. The primary end points were the occurrence of CVE (stroke, myocardial infarction or sudden death) and changes in the eGFR.

**Statistical methods**

Variables were compared using the t-test, the χ²-test, or an analysis of variance. The results were expressed as the mean ± s.d., and differences were considered statistically significant at P < 0.05. An assessment of the overall results was based on a survival analysis. The eGFR and BP data obtained after the onset of any disease (including a primary end point) were excluded from the analysis. Subgroups were divided based on eGFR values measured before and at the end of treatment. We used the Cox proportional hazards model to assess the relation between CVE and eGFR values. A multiple linear regression analysis was used to explore determinants of changes in eGFR; predictors of such changes (baseline eGFR, diabetes mellitus and stroke) were included in the original model. We used SAS software package Version 8.02 (SAS Institute, Cary, NC, USA) to perform all statistical analyses.

**RESULTS**

**Baseline characteristics**

The patients were divided into three groups: A, B and C, with eGFR <45, 45–59 and ≥60 ml min⁻¹ per 1.73 m², respectively. The baseline characteristics of the subjects are shown in Table 1. Approximately 11, 38 and 51% of the patients belonged to groups A, B and C, respectively. The majority of the CKD patients were in stage 3 (n = 3646); only a few were in stage 4 (n = 75) or 5 (n = 12). The CKD patients were older and had a higher prevalence of cerebrovascular and cardiovascular complications. Systolic blood pressure (SBP) and the prevalence of diabetes and dyslipidemia were similar among the groups. The rates of smoking and regular alcohol intake were lower in patients with CKD. Major concomitant drugs were similar in all groups, except for those in group A (the lowest eGFR); the patients in this group took more diuretics and uric acid–lowering drugs compared with those in the other two groups. Antihypertensive and lipid-lowering drugs were the most frequently used concomitant drugs in all patients, and calcium antagonists were prescribed for 9.2% of patients.

**Blood pressure and urinary protein excretion**

The mean SBP/diastolic BP decreased similarly in the three groups, and BP was well-controlled throughout the study period. In group A, the SBP/diastolic BP decreased from 165.6 ± 17.3/90.2 ± 11.8 mm Hg at baseline to 145.7 ± 16.5/80.8 ± 10.8 mm Hg after 3 months and to 139.9 ± 16.9/79.8 ± 10.9 mm Hg after 60 months of treatment. In group B, the SBP/diastolic BP decreased from 165.3 ± 16.5/93.2 ± 11.1 mm Hg to 145.6 ± 15.5/83.1 ± 10.3 mm Hg after 3 months and to 135.3 ± 11.9/76.7 ± 8.4 mm Hg after 60 months. In group C, the SBP/diastolic BP decreased from 165.3 ± 16.4/94.9 ± 11.3 mm Hg to 144.8 ± 15.6/84.1 ± 10.4 mm Hg after 3 months and to 135.4 ± 10.8/79.5 ± 8.8 mm Hg after 60 months.

The percentage of patients with positive urinary protein (≥ or above with dipstick test) decreased from 19.7% at baseline to 7.9% at the end of treatment. Improvement was apparent at 6 months, and continued throughout the treatment period.

**Changes in eGFR**

Changes in eGFR are shown in Figure 1. In group C, the eGFR slightly decreased initially from a baseline value of 74.7 ± 15.8 ml min⁻¹ per 1.73 m² (by 2.7 ml min⁻¹ per 1.73 m² at 1 year) and then gradually increased to a final value of 80.7 ± 23.3 ml min⁻¹ per 1.73 m² at the end of the study. In group B, the eGFR increased steadily from 52.8 ± 4.1 to 67.5 ± 15.7 ml min⁻¹ per 1.73 m², while it increased from 38.1 ± 6.7 to 57.6 ± 18.1 ml min⁻¹ per 1.73 m² in group A.

**Relationship between eGFR and CVE**

A total of 141 CVEs occurred, including 103 strokes and 38 myocardial infarcts. We analyzed the incidence of CVEs according to the eGFR at baseline as well as at the end of treatment (Table 2). The event rate became higher as the baseline eGFR declined. The relative risk (RR) of CVE in group A patients was 2.81 (95% confidence interval (CI), 1.80–4.39; P < 0.001) compared with that of group C patients. The final eGFR values had even stronger influences on the rate of CVE than the baseline eGFR value did. Compared with the event rate in patients with a final eGFR ≥60 ml min⁻¹ per 1.73 m², the RRs for CVE in the patients with a final eGFR <45 and 45–59 ml min⁻¹ per 1.73 m² were 3.24 (95% CI 2.06–5.08; P < 0.001) and 2.25 (95% CI 1.54–3.28; P < 0.001), respectively.

We also analyzed the incidence of CVE according to changes in the eGFR. Decreases in the eGFR were associated with higher event rates as compared with those observed in patients with an increase or no change in the eGFR. This was particularly evident in group A patients with a baseline eGFR <45 ml min⁻¹ per 1.73 m².
Concomitant drugs (%)

| Drug Type                        | 45 ≤ eGFR < 60 | eGFR ≥ 60 | Total | Exploratory P-value |
|----------------------------------|----------------|-----------|-------|----------------------|
| Antihypertensive drugs           |                |           |       |                      |
| Antihypertensive drugs           |                |           |       |                      |
| Calcium antagonist               | 8.8            | 8.8       | 9.5   | 9.2                  | 0.586                |
| β-Blocker                        | 1.5            | 1.5       | 1.5   | 1.5                  | 0.996                |
| ACE inhibitor                    | 0.4            | 0.6       | 0.5   | 0.5                  | 0.0757               |
| Diuretics                        | 2.9            | 1.4       | 1.3   | 1.5                  | 0.002                |
| Lipid-lowering drug              | 13.5           | 15.4      | 14.4  | 14.7                 | 0.286                |
| Antidiabetic drug                | 5.4            | 5.2       | 5.9   | 5.5                  | 0.470                |
| Uric acid–lowering drug          | 5.2            | 2.9       | 1.9   | 2.7                  | <0.001               |

**Table 1 Baseline demographics of study patients**

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Data are means ± S.D.

*S* < 0.001.

Figure 1 Serial changes in the estimated glomerular filtration rate (eGFR) in hypertensive patients with or without chronic kidney disease.

Serum uric acid and CVD

In group A, SUA decreased significantly from 5.81 ± 1.56 mg dl⁻¹ at baseline to 5.53 ± 1.50 mg dl⁻¹ at 6 months and remained at the same level thereafter. In groups B and C, SUA dropped from a baseline value of 5.31 ± 1.53 to 5.21 ± 1.51 mg dl⁻¹ and 5.03 ± 1.37 mg dl⁻¹ after 6 months of treatment, respectively.

Table 3 shows the demographics of the patients according to the change in SUA from baseline to 1 year of losartan treatment. Of note, the baseline SUA was higher in patients whose SUA decreased more than 0.5 mg dl⁻¹ compared with patients whose SUA remained unchanged or increased. In addition, there were large differences in final change in the eGFR from baseline to the end of follow-up, and the increase in the eGFR was greatest in the group with SUA decrement greater than 0.5 mg dl⁻¹.

The impact of hyperuricemia (SUA ≥ 7 mg dl⁻¹) on CVE was first examined in the overall patient population. The CVE rate was found to be 2.06 (95% CI 1.21–3.52; *P* = 0.008) times higher in the patients with hyperuricemia than in those without hyperuricemia. Figure 2 shows the CVE rate stratified by the eGFR in the presence and absence of hyperuricemia. In the absence of hyperuricemia (SUA < 7 mg dl⁻¹), the CVE rate was 10.83, 4.98 and 4.21/1000 person-years in groups A, B and C, respectively; the event rate was significantly (*P* = 0.003) higher in group A as compared with groups B and C, while it was similar in groups B and C. In the presence of hyperuricemia, however, the event rate in group B (17.02) was as high as that of group A (14.18), and it was significantly (*P* < 0.01) higher than that of group C (5.93). Thus, hyperuricemia increased the risk of CVE only in group B (RR 3.43 (95% CI 1.55–7.60); *P* = 0.002).

To examine possible influences of uric acid–lowering drugs and/or diuretics on the relationship between hyperuricemia and CVE, we performed the same analyses excluding those patients taking any of these drugs. The results were essentially the same, in which hyperuricemia increased the risk of CVE only in group B (RR 2.81 (95% CI 1.07–7.33); *P* = 0.036), but not in group A (RR 1.36 (95% CI 0.46–4.01); *P* = 0.38) or group C (RR 1.58 (95% CI 0.56–4.47); *P* = 0.392).
Parameters associated with changes in GFR
To explore the factors that may contribute to the observed improvement in eGFR, we performed a multiple linear regression analysis for changes in the eGFR. As shown in Table 4, the SBP during treatment, the SUA during treatment, the change (Δ) in SUA at 1 year and in urinary protein at 1 year were all significantly associated with a ΔeGFR from baseline to the end of the study in all three groups. ΔSUA and proteinuria stage at 1 year were predictive factors when the model included SBP throughout the study period, ΔSUA and proteinuria stage at 1 year. Therefore, ΔSUA and proteinuria stage were confirmed to be independent predictors of ΔeGFR from baseline to the end of the study.

The correlations between ΔSUA at 1 year and ΔeGFR from baseline to the end of the study, in both CKD and non-CKD patients, were strong and negative. Each 1-mg decrease in SUA from baseline to 1 year was associated with final increases in the eGFR of 2.71 ml min⁻¹ per 1.73 m² for the patients with a baseline eGFR <45 ml min⁻¹ per 1.73 m², 1.84 ml min⁻¹ per 1.73 m² for those with a baseline eGFR of 45–59 ml min⁻¹ per 1.73 m² and 1.31 ml min⁻¹ per 1.73 m² for those with a baseline eGFR ≥60 ml min⁻¹ per 1.73 m².

**DISCUSSION**
In the J-HEALTH study, hypertensive subjects were treated with losartan, an angiotensin-receptor blocker that has a unique uricosuric action. This subanalysis confirms that the baseline eGFR, as well as changes in the eGFR, have marked influences on cardiovascular mortality and morbidity. Hyperuricemia seems to enhance cardiovascular risks strongly in patients with an eGFR of 45–59 ml min⁻¹ per 1.73 m² (CKD stage 3A). An early reduction in SUA occurred before a substantial change in the eGFR, and this decline was closely associated with a future increase in the eGFR. Thus, SUA may have a role in the development of renal dysfunction in hypertensive patients.

In the recently modified classification of CKD by KDIGO, CKD stage 3 was subdivided into stages 3A and 3B, taking into consideration the epidemiological observations that cardiovascular risk increases sharply when the eGFR falls below 45 ml min⁻¹ per 1.73 m². Consistently, we also observed greatly increased CVE in patients with a baseline eGFR <45 ml min⁻¹ per 1.73 m². In addition, we observed that the RR of CVE increased in patients who had a decrease in eGFR, and this was particularly evident in those with a baseline eGFR <45 ml min⁻¹ per 1.73 m². These results indicate that not only the baseline eGFR but also the change in eGFR is an important determinant of CVE. Consistent with our study, Khan et al. reported that the rate of decline in the eGFR paralleled mortality in patients with left ventricular systolic dysfunction.

Few studies have examined the interaction of renal function and SUA in terms of cardiovascular risk, and the results of these studies are contradictory. Neri et al. reported that SUA was a strong independent correlate of CVE in CKD patients but not in non-CKD patients, whereas Navaneethan et al. reported that the presence of CKD attenuated the association of SUA with mortality. In this study, we examined the impact of hyperuricemia on CVE in three groups with an eGFR <45, 45–59 and ≥60 ml min⁻¹ per 1.73 m², because studies have established that there are clear differences in the CVE rate between CKD stages 3A and 3B. We observed that in the absence of hyperuricemia, the CVE rate was almost identical in those without CKD and in those with CKD stage 3A (Figure 2), suggesting that CKD stage 3A alone, without hyperuricemia, may not be a strong risk factor for CVE. However, once the patients with CKD stage 3A had hyperuricemia, the risk of CVE was dramatically elevated. This may suggest that hyperuricemia may account for much of the cardiovascular risk associated with CKD stage 3A. On the other hand,
hyperuricemia had no impact on CVE in those patients with an eGFR $\geq 60$ or $<45 \text{ ml min}^{-1} \text{ per 1.73 m}^2$. It may be that in patients with a very high risk of CVE, such as those with an eGFR $<45 \text{ ml min}^{-1} \text{ per 1.73 m}^2$, hyperuricemia may have few additional effects on enhancing CVE. Alternatively, in those with very low risk of CVE, such as those with an eGFR $\geq 60 \text{ ml min}^{-1} \text{ per 1.73 m}^2$, there may be few or no other factors with which hyperuricemia acts synergistically to enhance CVE risks. We recently found that the plasma methylglyoxal level is elevated in CKD and that it may be involved in vascular injury in animals and humans.23–25 Interestingly, uric acid has an amine residue that can react with the carbonyl residue in compounds such as methylglyoxal. In addition, oxidative stress and inflammation are enhanced even in the early stages of CKD.26 Thus, uric acid may exert negative effects in the stage 3A CKD patients by interacting synergistically with oxidative stress, inflammatory molecules and methylglyoxal.

Antihypertensive treatment with inhibitors of the renin–angiotensin system has been shown to reduce proteinuria and retard the rate of decline of renal function in hypertensive CKD patients.27,28 In this study, we have shown that losartan-based antihypertensive treatment can increase the eGFR in hypertensive patients. Further analyses of the factors associated with changes in the eGFR identified changes in SUA as a novel risk factor, in addition to the well-known risk factors for the decline of renal function.29,30 It is of note that a change in SUA was as powerful a risk factor as proteinuria status, which has been shown to be the strongest risk factor for end-stage renal failure. An early reduction of SUA from baseline to 1 year was strongly correlated with a future increase in the eGFR from baseline to the end of the study. Because the decreases in SUA occurred with few changes in eGFR, it may not be secondary to an increased eGFR. It may be assumed that decreases in SUA induced by losartan improved renal function in the present study. Indeed, studies have reported that

**Figure 2** Impact of hyperuricemia on cardiovascular event rate. eGFR, estimated glomerular filtration rate.

**Table 4** Multiple linear regression analysis for change in eGFR

| Factor                        | eGFR at baseline $<45$ | P-value | Parameter estimates | P-value | Parameter estimates | P-value |
|-------------------------------|------------------------|---------|---------------------|---------|---------------------|---------|
| Age (10 years)                | $-1.88 \pm 0.48$       | $<0.001$| $-1.80 \pm 0.26$   | $<0.001$| $-3.21 \pm 0.29$   | $<0.001$|
| Male sex                      | $-3.50 \pm 1.05$       | 0.001   | $-2.74 \pm 0.54$   | $<0.001$| $1.24 \pm 0.67$   | 0.065   |
| SBP at baseline (10 mm Hg)    | $-0.06 \pm 0.28$       | 0.831   | $-0.07 \pm 0.16$   | 0.660   | $-0.24 \pm 0.20$   | 0.229   |
| DBP at baseline (10 mm Hg)    | $0.09 \pm 0.41$        | 0.027   | $0.51 \pm 0.24$    | 0.034   | $0.55 \pm 0.30$   | 0.064   |
| SBP during treatment (10 mm Hg)| $-1.18 \pm 0.41$      | 0.005   | $-0.50 \pm 0.24$   | 0.039   | $-1.27 \pm 0.31$  | $<0.001$|
| DBP during treatment (10 mm Hg)| $0.52 \pm 0.63$        | 0.407   | $0.11 \pm 0.34$    | 0.751   | $0.47 \pm 0.42$ | 0.269   |
| Uric acid at baseline (mg dl$^{-1}$) | $-12.7 \pm 0.33$  | $<0.001$| $-0.75 \pm 0.18$   | $<0.001$| $-0.02 \pm 0.24$ | 0.949   |
| Uric acid during treatment (mg dl$^{-1}$) | $-3.25 \pm 0.39$  | $<0.001$| $-2.15 \pm 0.23$   | $<0.001$| $-1.18 \pm 0.30$ | $<0.001$|
| Uric acid change at 1 year (mg dl$^{-1}$) | $-2.71 \pm 0.46$  | $<0.001$| $-1.84 \pm 0.28$   | $<0.001$| $-1.31 \pm 0.41$ | 0.001   |
| Urinary protein at 1 year     | $-3.76 \pm 0.65$       | 0.001   | $-2.61 \pm 0.46$   | $<0.001$| $-1.72 \pm 0.79$ | 0.031   |

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure. Adjusted for eGFR at baseline, diabetes mellitus, and cerebrovascular, cardiovascular and hepatic disease. Data are means $\pm$ s.d.
allopurinol reduced SUA and retarded the progression of renal dysfunction.31–33 The importance of the reduction of SUA in long-term renal risk reduction was also confirmed in a post-hoc analysis of 1342 patients with type 2 diabetes mellitus and nephropathy in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) study.34 Taken together with these studies, our study provides strong support for the role of SUA in kidney damage in hypertensive patients.

The mechanism by which a decrease in SUA results in improved renal function is not clear from the present study. Experimental studies have shown that hyperuricemia causes endothelial, arteriolar and tubular interstitial damage in the kidney by increasing oxidative stress and inflammation.5,36 Price et al.37 reported that uric acid is transported into endothelial cells via urate reabsorptive transporter-1, and it then induces oxidative stress. In addition, it has been reported that hyperuricemia increases juxtaglomerular renin expression and decreases macula densa neuronal nitric oxide synthase expression.36 Thus, uric acid may cause renal injury by interacting synergistically with the renin–angiotensin system, oxidative stress and inflammatory molecules.

Our study has several limitations. The first is its observational design, which precludes the assignment of causation. Although BP levels were well-matched among the three groups, the medications used in addition to the initial 25–50 mg dose of losartan were prescribed at the discretion of participating physicians. We did not set a specific target BP or rules for additional drugs nor were we able to centralize the measurement of serum creatinine. Various guidelines for hypertension treatment recommend a target BP for CKD patients of <130/80 mm Hg. However, we could not achieve this goal. In addition, the CVE rate was low, particularly among non-CKD patients, which may have obscured the potential effects of hyperuricemia on CVEs.

In conclusion, the J-HEALTH study has demonstrated that losartan-based antihypertensive treatment increases the eGFR and reduces BP, proteinuria and SUA. The early reduction of SUA may predict future improvement of renal function, and the improvement of renal function greatly affects the occurrence of CVE, particularly in CKD patients. Hyperuricemia seems to be a major contributor to increased cardiovascular risks in early-stage CKD. These findings may be relevant to evaluating and managing cardiovascular risks in CKD patients. Further investigations are needed to clarify the role of uric acid in the pathophysiology of CKD.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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