Association Between J-Point Elevation and Death From Coronary Artery Disease – 15-Year Follow-up of the NIPPON DATA90 –

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Background: An early repolarization pattern, characterized by an elevation of the QRS-ST junction (J-point) on 12-lead electrocardiography (ECG) is associated with cardiac and sudden death. However, little is known about the prognostic significance of J-point elevation for various disease-specific cardiovascular outcomes, including coronary artery disease (CAD).

Methods and Results: To investigate the association between the presence of J-point elevation $\geq 0.1$ mV and various disease-specific cardiovascular outcomes, we conducted a 15-year prospective study in a representative general Japanese population of 7,630 individuals (41% men, mean age 52.4 years) who participated in the National Survey of Circulatory Disorders. Cox models were used to estimate the hazard ratios (HRs) adjusted for possible confounding factors. J-point elevation was present in 264 individuals (3.5%) and was associated with an increased risk of cardiac death (adjusted HR, 2.54; 95% confidence interval [CI] 1.40–4.58; P=0.002) and death from CAD (adjusted HR, 4.66; 95% CI 2.30–9.46; P<0.001). In a subgroup analysis by age, the association between J-point elevation and cardiovascular outcomes was more remarkable in middle-aged (<60 years) than in older individuals ($\geq$60 years) (all P for interaction $<$0.05).

Conclusions: J-point elevation on standard 12-lead ECG was an independent predictor of cardiac death and death from CAD in a representative sample of the general Japanese population, particularly among the middle-aged. (Circ J 2013; 77: 1260–1266)

Key Words: Cardiovascular diseases; Coronary artery disease; Electrocardiography; Epidemiology; J-point

Early repolarization, characterized by an elevation of the QRS-ST junction (i.e., the J-point) on 12-lead electrocardiography (ECG), is a common finding,¹ and has been considered clinically benign since it was first reported in 1936.² However, recent prospective studies in the general population have demonstrated that J-point elevation is associated with an increased risk of cardiac³,⁴ and sudden death.⁵,⁶ Following the publication of those studies, a number of reviews have speculated that several mechanisms underlie the association between J-point elevation and cardiac and arrhythmic death.⁷–⁹ However, it remains controversial whether the J-point elevation is a manifestation of structural heart disease, such as coronary artery disease (CAD),¹⁰–¹³ or primary electrical abnormalities.¹⁴–¹⁶ Furthermore, little is known about the prognostic significance of a J-point elevation for various disease-specific cardiovascular outcomes, including CAD.
Therefore, a 15-year prospective study was conducted to investigate the long-term prognosis associated with J-point elevation in a representative sample of the general Japanese population aged 30 years or older who participated in the National Survey on Circulatory Disorders.

Methods

Study Design

Cohort studies of the National Survey on Circulatory Disorders and the National Nutrition Survey of Japan conducted in 1980 and 1990, respectively, by the Ministry of Health and Welfare are known as NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged). We analyzed data from NIPPON DATA90 using the baseline survey conducted in 1990. The detailed methods are described elsewhere.17-19 The present study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000; No. 17-21-1, 2010).

Study Participants

Members of an overall population (n=10,956) aged ≥30 years from 300 randomly selected health districts throughout Japan were invited to participate in the study. Among them, 8,383 community-based individuals agreed and the participation rate was 76.5% (8,383 of 10,956) before exclusion for the reasons indicated below. The survey consisted of a physical examination, blood test, self-administered questionnaire on lifestyle, dietary assessment, and standard 12-lead ECG recording. For the present study, participants were followed up to 2005 (NIPPON DATA90, 1990-2005).

A total of 753 participants were excluded from this analysis for the following reasons: previous myocardial infarction (MI) or stroke at baseline (n=247); major conduction defects on ECG (QRS duration ≥120 ms) or Brugada-type ECG20-21 (n=172); and no ECG measurements at baseline (n=334). Thus, 7,630 individuals were included in the analysis (3,108 men; mean age 52.4 years, range 30–95 years).

Endpoint Determination

To determine the cause of death during the 15-year follow-up, the National Vital Statistics database of Japan was used with permission from the Management and Coordination Agency, Government of Japan. The underlying causes of death in the National Vital Statistics database of Japan was used with permission from the Management and Coordination Agency, Government of Japan. The detailed methods are described elsewhere.17-19 Codes that showed agreement between the two researchers’ assessments were accepted; codes that showed disagreement were adjudicated by a panel of epidemiologists and cardiologists. J-point elevation was defined as an elevation of the QRS-ST junction (J-point) in at least one lead according to MC9.2 as follows: in the inferior (II, III, aVF) and lateral leads (I, aVL, V6), an elevation of the J-point ≥0.1 mV from baseline; in the anterior leads (V1-6), an elevation of the J-point ≥0.2 mV in leads V1-4 and ≥0.1 mV in lead V5. Participants with major conduction defects on ECG (QRS duration ≥120 ms) were not included in this definition. ECG findings that we examined were also Q wave abnormality (MC1.1–1.3), left ventricular hypertrophy (LVH: MC3.1 or 3.3), major ST depression (MC4.1–4.3), major T-abnormality (MC5.1 or 5.2).22

Non-fasting blood samples were obtained, and the serum was separated and centrifuged immediately after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. Serum total cholesterol was measured enzymatically. Lipid measurements were standardized using the Lipids Standardization Program from the Centers for Disease Control-National Heart, Lung and Blood Institute. Hemoglobin A1c was determined by a latex cohesion method. All samples were shipped to a central laboratory (SRL, Tokyo, Japan) for measurements.

Statistical Analysis

Baseline characteristics of participants are presented as means and standard deviations for continuous variables and percentages for categorical variables. A comparison of baseline characteristics between each J-point elevation was made using statistical tests, such as the unpaired Student’s t-test, Wilcoxon signed-rank test, and the chi-square test. Kaplan-Meier curves were plotted according to the presence or absence of J-point elevation, and differences between groups were examined by log-rank test. Cox proportional-hazard regression models were used to estimate the multivariate adjusted HRs of J-point elevation for mortality, as compared with an absence of J-point elevation. Model 1 was adjusted for age and sex; model 2 was adjusted for the same confounding factors as those used in a Finnish study3 (ie, age, sex, BMI, smoking status, medication status, systolic BP, heart rate, LVH on ECG (classified according to MC3.1 or 3.3), and suspected CAD on ECG (classified according to MC1.1–1.3, 5.1–5.2, or 4.1–4.3); model 3 was adjusted for drinking habit, serum total cholesterol, and hemoglobin A1c in addition to the variables adjusted in Model 2. We also compared the prognostic significance of J-point elevation with other ECG risk markers such as suspected CAD
and LVH.\textsuperscript{3} A subgroup analysis was conducted according to age (<60 years, ≥60 years) on the basis of the Finnish study,\textsuperscript{1} which examined parameters in subjects aged 30–59 years. Tests for interaction were performed by introducing a multiplicative interaction term into the main models. The statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Cary, NC, USA). All probability values were 2-sided.

The interaction by age was significant for cardiovascular death (P for interaction <0.05) and death from CAD (both Ps for interaction <0.05) (Table 4). In the subgroup analysis by age, a more pronounced association between J-point elevation and cardiovascular outcomes was evident in middle-aged individuals (<60 years) compared with older individuals (≥60 years). The test for multiplicative interaction by age was significant for cardiovascular death (P for interaction <0.01), as well as for cardiac death and death from CAD (both Ps for interaction <0.05).

Results

Baseline characteristics of the individuals with and without J-point elevation are presented in Table 1. Overall, a J-point elevation was present in 264 of 7,630 individuals (3.5%); in the anterior leads in 240 (3.1%) individuals, and in the inferior or lateral leads in 24 (0.3%) subjects. Individuals with J-point elevation were more often male, younger, smokers, alcohol drinkers, with higher diastolic BP, lower heart rate, and more likely to have a LVH on ECG than those without J-point elevation. Baseline characteristics of men with and without J-point elevation are also presented in Table S1: 95.8% of individuals with J-point elevation were men.

During the 15-year follow-up, 1,159 subjects died and of these, 325 died from cardiovascular causes. Among the cardiovascular deaths, 173 individuals died from cardiac causes, and 136 died from stroke. Among the cases of cardiac death, 71 subjects died from CAD (59 from acute MI, 83.1%), 66 died from heart failure, and only 12 died from arrhythmia.

Figure demonstrates the Kaplan-Meier analysis of individuals with and without J-point elevation. For those with J-point elevation, the death rate appeared to diverge from those without J-point elevation after 8 years of follow-up. There were no significant differences between the 2 groups in terms of cardiovascular death, though the difference tended to increase with time (Figure A). Individuals with J-point elevation had significantly higher rates of cardiac death and death from CAD than those without J-point elevation (Figures B, C).

Results of the multiple Cox proportional-hazard regression models are presented in Table 2. Individuals with J-point elevation had a significantly higher risk of cardiovascular death than those without J-point elevation in Model 1. In Models 2 and 3, statistical significance was lost, but the point estimate was only slightly lower than that in Model 1 (HR in Model 2=1.48; P=0.042; and 3=1.49; P=0.136). With respect to cardiac death and death from CAD, individuals with J-point elevation had a markedly elevated risk compared with those without J-point elevation across each model (HRs in Model 3=2.54 for cardiac death, P=0.002; and 4.66 for death from CAD, P<0.001). We did not calculate HRs for death from heart failure, arrhythmia, and stroke owing to the small number of deaths: only 1 person died from each cause among the individuals with J-point elevation (Table S2). The results were similar when analyses were restricted to men (Table S3).

The comparative analysis of the prognostic value of ECG findings showed an increased risk for cardiac death among individuals with suspected CAD on ECG (adjusted HR=1.72; P=0.039) and among those with LVH on ECG (adjusted HR=1.48; P=0.042) (Table 3).

In the subgroup analysis by age, a more pronounced association between J-point elevation and cardiovascular outcomes was evident in middle-aged individuals (<60 years) compared with older individuals (≥60 years). The test for multiplicative interaction by age was significant for cardiovascular death (P for interaction <0.01), as well as for cardiac death and death from CAD (both Ps for interaction <0.05) (Table 4).

Table 1. Baseline Characteristics of Study Participants in NIPPON DATA90

|                      | No J-point elevation | J-point elevation | P value |
|----------------------|----------------------|-------------------|---------|
| n (%)                | 7,366 (96.5)         | 264 (3.5)         |<0.001  |
| Men                  | 2,855 (38.8)         | 253 (96.8)        |<0.001  |
| Age, mean (SD), (years) | 52.5 (13.7)        | 49.4 (12.6)       |<0.001  |
| Previous smoker      | 759 (10.3)           | 62 (23.5)         |<0.001  |
| Current smoker       | 2,012 (27.3)         | 142 (53.8)        |<0.001  |
| Alcohol drinker      | 1,949 (26.5)         | 167 (63.3)        |<0.001  |
| BMI, mean (SD), (kg/m²) | 22.9 (3.2)           | 22.7 (2.7)        |0.415   |
| Serum TC, mean (SD), (mg/dl) | 203.3 (37.9)     | 201.1 (35.8)      |0.364   |
| Hemoglobin A₁c, mean (SD), (%) | 4.9 (0.7)          | 5.0 (0.9)         |0.143   |
| BP, mean (SD), (mmHg) |                     |                   |         |
| Systolic             | 134.9 (20.5)         | 136.5 (20.8)      |0.178   |
| Diastolic            | 81.1 (11.8)          | 83.6 (13.4)       |<0.001  |
| Antihypertensive drug user | 1,027 (13.9)   | 36 (13.6)         |0.888   |
| Bradycardia (heart rate ≤50beats/min) on ECG | 108 (1.5)       | 8 (3.0)           |0.047   |
| LVH on ECG*          | 755 (10.2)           | 86 (32.6)         |<0.001  |
| Suspected CAD on ECG† | 334 (4.5)            | 13 (4.9)          |0.765   |

Data are n (%) unless otherwise stated. *Diagnosis of LVH based on Minnesota Codes 3.1 or 3.3. †Suspicion of CAD based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3. BMI, body mass index; TC, total cholesterol; BP, blood pressure; ECG, electrocardiography; CAD, coronary artery disease; LVH, left ventricular hypertrophy.
J-Point Elevation and Death From CAD

Discussion

The results of this 15-year prospective study of a representative sample of the general Japanese population suggest that J-point elevation on a standard 12-lead ECG is significantly associated with an increased risk of death from cardiac causes, particularly from CAD after adjustment for possible confounding factors. J-point elevation was a stronger predictor of death from cardiac causes and CAD than other ECG risk markers such as suspected CAD and LVH. Furthermore, the association was more apparent in middle-aged individuals. To our knowledge, this is the first community-based study to reveal a relationship between J-point elevation and death from CAD.

Comparison With Previous Studies

Our data are consistent with those from recent community-based studies. In the present study, individuals with J-point elevation had a remarkably elevated risk of death from CAD. Conversely, recent studies in general Finnish, German, and US populations demonstrated that J-point elevation was associ-

Figure. (A-C) Kaplan-Meier curves for cardiovascular outcomes according to the presence of J-point elevation in participants in NIPPON DATA90. Blue and red lines indicate individuals without and with J-point elevation, respectively. For those with J-point elevation, the death rate appears to diverge from those without J-point elevation after 8 years’ follow-up.
and it included such predictors of cardiovascular death as the classical risk factors and confounding ECG findings. However, in previous studies, although some risk factors were adjusted for in the multivariate analysis, other major risk factors, such as drinking habit, serum total cholesterol, and hemoglobin A1c in the Finnish study, and confounding ECG findings in the German study, were not adjusted. Furthermore, both classical risk factors and confounding ECG findings were not adjusted for in a recent Japanese study by Haruta et al., which curiously reported that J-point elevation was associated with an increased risk of cardiac death, although the details of the cardiac death were not described. However, other studies and their national statistics reports found that CAD was the most common cause of cardiac death in each country, which suggests that J-point elevation may also have been associated with an increased risk of death from CAD in the Finnish, German, and US studies. The present study found a significant association between J-point elevation and increased risk of death from cardiac causes, particularly from CAD, after multivariate adjustment, and it included such predictors of cardiovascular death as the classical risk factors and confounding ECG findings. However, in previous studies, although some risk factors were adjusted for in the multivariate analysis, other major risk factors, such as drinking habit, serum total cholesterol, and hemoglobin A1c in the Finnish study and confounding ECG findings in the German study, were not adjusted. Furthermore, both classical risk factors and confounding ECG findings were not adjusted for in a recent Japanese study by Haruta et al. which curiously reported that J-point elevation was associated with

| Cardiovascular deaths | No J-point elevation | J-point elevation | P value |
|-----------------------|----------------------|------------------|---------|
| n (%)                 | 311 (4.2)            | 18 (6.8)         |         |
| Model 1 HR (95% CI)   | 1.00                 | 1.86 (1.14–3.03) | 0.013   |
| Model 2 HR (95% CI)   | 1.00                 | 1.55 (0.93–2.57) | 0.092   |
| Model 3 HR (95% CI)   | 1.00                 | 1.49 (0.88–2.50) | 0.136   |

| Cardiac deaths        | n (%)                |                 |         |
|-----------------------|----------------------|-----------------|---------|
| n (%)                 | 159 (2.2)            | 14 (5.3)        |         |
| Model 1 HR (95% CI)   | 1.00                 | 2.79 (1.58–4.93)| <0.001  |
| Model 2 HR (95% CI)   | 1.00                 | 2.58 (1.43–4.65)| 0.002   |
| Model 3 HR (95% CI)   | 1.00                 | 2.54 (1.40–4.58)| 0.002   |

| Deaths from CAD       | n (%)                |                 |         |
|-----------------------|----------------------|-----------------|---------|
| n (%)                 | 60 (0.8)             | 11 (4.2)        |         |
| Model 1 HR (95% CI)   | 1.00                 | 4.61 (2.35–9.04)| <0.001  |
| Model 2 HR (95% CI)   | 1.00                 | 4.74 (2.35–9.56)| <0.001  |
| Model 3 HR (95% CI)   | 1.00                 | 4.66 (2.30–9.46)| <0.001  |

Model 1 adjusted for age and sex. Model 2 adjusted for the same confounding factors used in a Finnish study: age, sex, BMI, smoking status, medication status, systolic BP, heart rate, LVH on ECG (based on Minnesota Codes 3.1 or 3.3), and suspected CAD on ECG (based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3). Model 3 adjusted for drinking habits, serum TC, and hemoglobin A1c in addition to the factors adjusted in Model 2. HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

| Cardiovascular death  | J-point elevation (n=264) | Suspected CAD (n=347) | LVH (n=841) |
|-----------------------|---------------------------|-----------------------|-------------|
|                      | Adjusted HR (95% CI)      | Adjusted HR (95% CI)  | Adjusted HR (95% CI) |
|                      | P value                   | P value                | P value     |
| Cardiovascular death  | 1.49 (0.88–2.50)          | 1.53 (1.05–2.25)      | 1.45 (1.09–1.92) |
|                      | 0.136                     | 0.029                  | 0.010       |
| Cardiac death        | 2.54 (1.40–4.58)          | 1.72 (1.03–2.89)      | 1.48 (1.01–2.18) |
|                      | 0.002                     | 0.039                  | 0.042       |
| Death from CAD       | 4.66 (2.30–9.46)          | <0.001                 | 1.34 (0.73–2.45) |
|                      | 0.304                     | 0.353                  |

HRs adjusted for age, sex, BMI, smoking status, medication status, systolic BP, drinking habit, serum TC, hemoglobin A1c, heart rate, LVH on ECG (based on Minnesota Codes 3.1 or 3.3), and suspected CAD on ECG (based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3). Abbreviations as in Tables 1, 2.

| Subgroup Analysis by Age: Multivariate Adjusted HRs for an Association of J-Point Elevation With Various Cardiovascular Outcomes in a 15-Year Follow-up Study (NIPPON DATA90) |
|-----------------------------------------------|----------------|---------------|---------------|
| No. at risk (≥60 years) | No. of J-point elevation | No. of deaths | Cardiovascular deaths |
| Number | Number | Number | Adjusted HR* (95% CI) | P for interaction |
|--------|--------|--------|-----------------------|------------------|
| 5,197  | 203    | 57     | 3.87 (1.85–8.10)†    | 0.003            |
| ≥60 years | 2,433 | 61     | 0.79 (0.36–1.75)     | 0.010            |

HRs adjusted for age, sex, BMI, smoking status, medication status, systolic BP, drinking habit, serum TC, hemoglobin A1c, heart rate, LVH on ECG (based on Minnesota Codes 3.1 or 3.3), and suspected CAD on ECG (based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3). Significant differences in the HRs: †P<0.001. Abbreviations as in Tables 1, 2.
decreased risk of cardiac death. Interestingly, in the present study, even after adjusting for all of the above factors, J-point elevation was still found to be an independent predictor of death from cardiac causes and CAD.

In the present study, J-point elevation, the definition of which according to MC9.2 is different from that used in other studies, was related to an increased risk of death from cardiac causes, particularly from CAD. Likewise, Olson et al used a similar definition to ours (including J-point elevation in the anterior leads and 1 lead affection) and reported that J-point elevation was significantly predictive of sudden cardiac death, primarily of the atherosclerotic type. Our results also support ischemia-induced J-point elevation was observed in any lead of ECG. Therefore, it may be reasonable to analyze the association of J-point elevation in any lead with cardiovascular outcomes, particularly CAD. In addition, consistent with previous studies, J-point elevation in the inferior or lateral leads was a better predictor of increased risk of death from cardiovascular causes (including CAD) in the middle-aged group (<60 years).

Consistent with previous reports of 0.9–12.3% prevalence of J-point elevation, the overall prevalence of J-point elevation in the present study was 3.5% (8.1% for males, 0.2% for females). These values are quite low compared with another Japanese population in which incident J-point elevation during the follow-up was found in 779 cases (13.0%) and prevalent J-point elevation in 650 cases (10.9%), resulting in a total prevalence of 23.9%. Variation in estimates may be related to differences in trait definition, adjudication technique, and study sample demographics. For instance, the study describing the clinical correlates and heritability of J-point elevation in 2 large, population-based cohorts (Framingham Heart Study and Health 2000 Survey) demonstrated that participants in the Framingham Heart Study (mean age, 40 years) were approximately 10 years younger than those in the Health 2000 Survey cohort (mean age, 50 years) and the prevalence of J-point elevation was nearly twice as high (6.1% and 3.2%, respectively). Therefore, the disparity in the prevalence of J-point elevation may result from differences between the Nagasaki study by Haruta et al and our study in the participants’ ages. The population reported by Haruta et al was much younger (participants <40 years were 58.2%) compared with our study (21.9%). Interestingly, the mean ages of participants in our study (participants with and without J-point elevation: 49.4 and 52.5 years, respectively) were almost the same as those in the Health 2000 Survey and the prevalence of J-point elevation is very similar (3.5% and 3.2%, respectively).

Potential Mechanisms
The exact mechanisms for the association between J-point elevation and cardiovascular outcomes remain unclear. One possible interpretation for this association may be in the finding of several studies where J-point elevation on ECG represented a peri-infarction block, which usually suggests left CAD. However, previous experimental studies have indicated that the mechanism for J-point elevation is related to fatal arrhythmia. Specifically, it was found that heterogeneity in ventricular repolarization manifests either as an early repolarization or J-point elevation on ECG, resulted in a vulnerability to ventricular arrhythmia. Accordingly, it is possible that J-point elevation may derive from either structural heart disease, such as CAD, or primary electrical abnormalities, both of which produce vulnerability to serious ventricular arrhythmia and sudden death. However, the Japanese population has a very low rate of sudden death compared with Western populations. Thus, in the present study, we did not observe a sufficient number of arrhythmic deaths, as opposed to the significant association between J-point elevation and death from CAD. Further studies are required to clarify the potential mechanisms underlying the association between J-point elevation and cardiovascular outcomes, as well as the difference in the prognostic value for death from CAD between J-point elevation and suspected CAD on ECG.

Study Limitations
First, the number of deaths was too small to comprehensively analyze the prognostic significance of arrhythmia associated with J-point elevation. During the 15-year follow-up, we observed a lower prevalence of J-point elevation and mortality than that found by recent community-based studies. We calculated a wide range of HRs of J-point elevation, particularly in the inferior or lateral leads. Second, we did not have any incidence data, and as a result we could not examine whether there were any differences between incidence and mortality. Third, the use of death certificate data may lead to misclassification in the cause of death. It was reported that most cases of sudden cardiac death from arrhythmia tend to be described as CAD or heart failure on Japanese death certificates. Fourth, uncertainty around the cause of death from CAD, other than acute MI, may limit the present results. Lastly, we did not have detailed information on the amplitude or morphology of the J-point elevation (eg, notching or slurring, and horizontal/descending or rapidly ascending/upsloping in the ST segment). A rapidly ascending ST segment after J-point elevation appears to be a benign variant of early repolarization.

Conclusions
We demonstrated that J-point elevation on standard 12-lead ECG is an independent predictor of death from cardiac causes, particularly from CAD, in a representative sample of the general Japanese population. J-point elevation may be a useful marker for cardiac and CAD risk stratification. Future studies are necessary to disclose the potential mechanisms responsible for this association.

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### Supplementary Files

#### Supplementary File 1

**Table S1.** Baseline Characteristics of the Men in NIPPON DATA90

**Table S2.** Number of Deaths Among 3,108 Men and 4,522 Women According to the Presence of a J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

**Table S3.** HRs of Cardiovascular Outcomes in 3,108 Men According to the Presence of J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

**Table S4.** Subgroup Analysis of the Middle-Aged Group (≤60 Years) According to the Location of the J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

**Data S1.** Appendix

Please find supplementary file(s); http://dx.doi.org/10.1253/circ.12-1273

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