

Atrial fibrillation is associated with cardiovascular events in obese Japanese with one or more cardiovascular risk factors: The Japan Morning Surge Home Blood Pressure (J-HOP) Study

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Abstract

The impacts of atrial fibrillation (AF) and home blood pressure (BP) on the cardiovascular prognosis of obese individuals have not been clarified. We analyzed the differences in the prognosis (including the effect of the home BP of AF patients with/without obesity) in a Japanese population with cardiovascular risk factors. We enrolled 3,586 patients from the J-HOP study who had at least one cardiovascular risk factor. We conducted 12-lead electrocardiography, and the group of AF patients was determined as those whose electrocardiography revealed AF. Obesity was defined as a body mass index $>25 \text{ kg/m}^2$. The primary end points were fatal/nonfatal cardiovascular events (myocardial infarction, stroke, hospitalization for heart failure, and aortic dissection). Among the obese patients, those with AF ($n = 36$) suffered more significantly cardiovascular events (log rank 7.17, $p = .007$) compared to the patients with sinus rhythm ($n = 1,282$), but among the non-obese patients, the rates of cardiovascular events were similar (log rank 0.006, $p = .94$) in the AF patients ($n = 48$) and sinus rhythm patients ($n = 2220$). After adjusting for age, sex, office/home BP, smoking, diabetes, and creatinine level, AF was an independent predictor of cardiovascular events in the obese group (hazard ratio [HR] 3.05, 95%CI: 1.17-7.97, $p = .023$). Home systolic BP was also a predictor of cardiovascular events in the obese group independent of the risk of AF (per 10 mm Hg: HR 1.36, 95%CI: 1.02-1.83, $p = .039$). In conclusion, AF was an independent predictor of cardiovascular events in obese patients after adjusting for home BP.

1 | INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia in clinical settings, and the number of AF patients is increasing every year worldwide.¹ In the Framingham Heart Study, AF was associated with mortality.² The symptoms of AF affect an individual's quality of

life, and the presence of AF poses risks of cerebral embolism, heart failure, and dementia.^{3,4} AF is also strongly associated with arteriosclerosis risk factors such as hypertension, diabetes mellitus, and dyslipidemia.^{5,6} The addition of hypertension and diabetes mellitus to AF increases the risk of cerebral embolism and affects the prognosis.⁷

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Obesity has also been shown to be an independent risk factor for AF.⁸⁻¹² For example, in the long-term follow-up of the Framingham Heart Study, every unit increase in body mass index (BMI) raised the AF risk by 4%–5%.⁹ Obesity leads to left atrial remodeling by various mechanisms^{13,14} and is associated with a prominent increase in the risk of developing AF and a persistent or permanent form of AF.^{8,15}

Obesity also causes a risk of hypertension and presents with resistance hypertension.¹⁶⁻¹⁸ Hypertension also causes AF through left atrial remodeling.¹⁹ The impact of AF and home blood pressure to the cardiovascular prognosis in obesity has not been clarified. We conducted the present retrospective study to determine the differences in backgrounds and prognoses including the effect of the home blood pressure of AF patients with/without obesity among a population of Japanese patients with cardiovascular risk factors.

2 | METHODS

2.1 | Study design

The patients examined herein were enrolled in the J-HOP study, which is a prospective observational study of home blood pressure (BP) measurement that recruited patients from January 2005 to May 2012 from primary practices, hospital-based outpatient clinics, and university hospitals in Japan. The ethics committee of the internal review board of the Jichi Medical University School of Medicine, Tochigi, Japan approved the protocol of the J-HOP study. The present study protocol was registered on a clinical trials registration site (University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR): #UMIN00000894). All participants in this study provided written informed consent. The details of the design and methods of the J-HOP study have been reported elsewhere.²⁰ The J-HOP study enrolled 4,310 ambulatory patients with one or more of the following cardiovascular risk factors: hypertension, hyperlipidemia (total cholesterol level >240 mg/dl or treated with a drug), impaired glucose tolerance or diabetes mellitus (a fasting glucose level >126 mg/dl, a glycated hemoglobin level >6.1%, and/or treated), chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m²), metabolic syndrome, sleep apnea syndrome, AF, current smoking, chronic obstructive pulmonary disease, and history of cardiovascular disease (coronary artery disease, stroke, aortic dissection, peripheral artery disease, and/or congestive heart failure). Patients who had malignancy or chronic inflammatory disease were excluded.

In the present study, we obtained the electrocardiography (ECG) data of 3586 of the J-HOP patients. We divided the patients into two groups based on whether the patients were obese; obesity was defined as a body mass index (BMI) >25 kg/m². The BMI values were calculated as the patient's weight (kg)/height (m²) at baseline. Patients with AF were defined as those with documented AF on ECG at the participating institutions.

2.2 | 12-lead ECG and other measurements

ECG examinations were performed within three months after the patient's first visit at each institution, and with the paper speed of 25 mm/s and a gain of 10 mm/mV (or 5 mm/mV). At least two trained individuals who did not know the patient's condition or background assessed the ECGs parameters and evaluated the ECG rhythm as AF or sinus rhythm. Office BP was measured automatically three times at 15-sec intervals per visit with the patient in a seated position, using a validated oscillometric device (HEM-5001; Omron Healthcare, Kyoto, Japan).²¹ The mean values of six readings obtained at two clinic visits were used as the office BP.

Home BP was measured by same validated oscillometric device as that used for the office BP measurement, and we used the average of the patient's morning BP (within 1 hr of getting up and before taking antihypertensive medication) and evening BP (before going to bed) as the home BP value. Hypertension was defined as systolic BP (SBP) >140 mmHg and diastolic BP (DBP) >90 mmHg in office BP, and/or the use of antihypertensive medication. Blood samples were drawn for the analyses of the serum concentrations of fasting blood glucose, HbA1c, total cholesterol, triglyceride, and creatinine with the patient in a fasting state in the morning at study enrollment. All assays were performed at a single laboratory center (SRL, Tokyo, Japan) within 24 hour of the sample collection. The plasma level of brain natriuretic peptide (BNP) was measured by using a chemiluminescent enzyme (MI02 Shionogi BNP; Shionogi, Osaka, Japan).

2.3 | Ascertainment of events

We assessed a composite cardiovascular outcome during the study follow-up that included fatal and nonfatal coronary artery disease (acute myocardial infarction or angina pectoris requiring percutaneous coronary intervention), sudden death within 24 hour of the abrupt onset of symptoms, fatal and nonfatal stroke (except transient ischemic attack), fatal and hospitalized heart failure, and aortic dissection. If two or more such events occurred, we evaluated the first cardiovascular event in our analysis. When patients failed to come to the hospital, we interviewed them or their families or both by telephone. The end point committee adjudicated all events by reviewing the patients' files and source documents or by requesting more detailed written information from investigators. A final follow-up survey to reconfirm the clinical outcomes was performed from September 2014 to March 2015.

2.3.1 | Statistical analyses

All descriptive statistics data are presented as the mean ± standard deviation or median (25%, 75%) or proportions where appropriate. The χ^2 test was used to detect differences in the prevalence rate between groups. Student's t-test was performed to detect

differences in continuous variables of the baseline characteristics between the obese and non-obese groups. We compared the cumulative incidences of total cardiovascular events in the AF patients and patients with sinus rhythm divided into obese and non-obese groups. The Kaplan-Meier curves of the cumulative incidence of cardiovascular events in each group were calculated, and the differences in the rate of events between groups were assessed by the log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) of the incidences of total cardiovascular events were calculated using Cox regression analyses after adjustment for age, sex, office SBP/DBP, home SBP/DBP, smoking, diabetes mellitus, creatinine level, and AF in a multivariate analysis. All statistical analyses were performed with IBM SPSS Statistics ver. 21 software (IBM, Chicago, IL). Two-sided *p*-values <.05 were defined as significant.

3 | RESULTS

At baseline, the number of patients whose ECGs revealed sinus rhythm was 3,502, and the number of patients whose ECGs revealed AF was 84. Table 1 summarizes the baseline characteristics of the AF patients and patients with sinus rhythm divided into obese and non-obese groups. In both the obese and non-obese groups, the AF patients were significantly older and had a higher proportion of males, past history of heart failure, aspirin use, and warfarin use compared to the sinus rhythm patients. The home pulse rate (PR), serum creatinine level, and BNP level were significantly higher in the AF patients compared to those with sinus rhythm in both the obese and non-obese groups. Among the patients in the non-obese group, the office SBP and home SBP values were significantly lower in the AF patients compared to those with sinus rhythm (office

TABLE 1 Patients' characteristics

	Non-obese		<i>p</i> -value	Obese		<i>p</i> -value
	Sinus rhythm (n = 2,220)	AF (n = 48)		Sinus rhythm (n = 1,282)	AF (n = 36)	
Age, yrs	65.7 ± 10.3	69.2 ± 9.5	0.021	62.3 ± 11.1	69.3 ± 7.9	<0.001
Male, %	46.4	66.7	0.005	45.7	63.9	0.031
BMI, kg/m ²	22.2 ± 1.9	22.2 ± 1.9	0.99	27.7 ± 2.7	27.6 ± 3.5	0.74
Hypertension, %	89.4	77.1	0.007	93.7	86.1	0.071
Current smoking, %	13.0	14.6	0.74	11.0	13.9	0.59
Hyperlipidemia, %	23.0	18.8	0.48	30.0	30.6	0.94
Diabetes mellitus, %	17.9	8.3	0.086	23.8	16.7	0.32
Prior CAD, %	9.3	4.2	0.31	10.4	16.7	0.26
Prior stroke, %	4.3	2.1	0.72	3.6	16.7	0.002
Prior heart failure, %	1.5	8.3	0.007	1.4	8.3	0.017
β-blocker, %	13.0	27.1	0.009	15.4	13.9	1.0
Statin, %	21.8	12.5	0.16	28.0	25.0	0.85
Aspirin, %	15.1	35.4	0.001	16.0	30.6	0.036
Warfarin, %	1.8	41.7	<0.001	1.2	47.2	<0.001
Office SBP, mmHg	141.7 ± 16.4	136.8 ± 18.7	0.039	141.7 ± 16.1	138.9 ± 15.8	0.31
Office DBP, mm Hg	80.9 ± 10.4	83.2 ± 12.3	0.13	83.2 ± 10.2	83.1 ± 9.0	0.97
Office PR, /min	71.0 ± 10.7	78.4 ± 12.7	<0.001	71.5 ± 10.3	74.8 ± 10.8	0.052
Home SBP, mm Hg	133.2 ± 13.9	127.7 ± 14.7	0.006	136.7 ± 14.5	135.6 ± 13.5	0.65
Home DBP, mm Hg	74.9 ± 8.9	76.0 ± 10.6	0.41	78.5 ± 9.3	79.8 ± 8.0	0.39
Home PR, /min	67.5 ± 8.7	73.0 ± 11.6	<0.001	68.2 ± 8.5	72.0 ± 10.8	0.009
Glucose, mg/dl	106 ± 27	107 ± 21	0.73	111 ± 29	115 ± 40	0.37
HbA1c, %	5.8 ± 0.7	5.7 ± 0.4	0.53	6.0 ± 0.9	5.8 ± 0.6	0.35
Total cholesterol, mg/dl	203 ± 32	197 ± 36	0.20	203 ± 34	193 ± 35	0.096
Triglyceride, mg/dl	115 ± 76	117 ± 58	0.87	143 ± 94	137 ± 86	0.73
Creatinine, mg/dl	0.74 ± 0.24	0.85 ± 0.22	0.003	0.76 ± 0.26	0.87 ± 0.30	0.012
BNP, pg/ml	19.5 (9.6, 39.5)	107.0 (29.3, 170.8)	<0.001	14.5 (6.8, 28.8)	114.0 (38.4, 187.0)	<0.001

Note: Data are the mean ± SD or median (25%, 75%) or a percentage.

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; DBP, diastolic blood pressure; PR, pulse rate; SBP, systolic blood pressure.

SBP: 136.8 ± 18.7 vs. 141.7 ± 16.4 mm Hg, $p = .039$; home SBP: 127.7 ± 14.7 vs. 133.2 ± 13.9 mm Hg, $p = .006$).

The mean follow-up period was 60 ± 30 months. During the follow-up period, primary end points occurred in 87 patients (3.9%) in the sinus rhythm + non-obesity group, two patients (4.2%) in the AF + non-obesity group, 60 patients (4.7%) in the sinus rhythm + obesity group, and five patients (13.9%) in the AF + obesity group.

The Kaplan-Meier curves of the incidence of cardiovascular events are given in Figure 1. The patients in the AF + obesity group had significantly poorer prognoses compared to those in the sinus rhythm + obesity group (log rank 7.17, $p = .007$). There was no significant difference in the prognoses of the non-obese patients between those with sinus rhythm and those with AF (log rank 0.006, $p = .94$).

We used a Cox proportional hazard model to evaluate the risk of cardiovascular events (Table 2). The results demonstrated that in the obese patients, AF was an independent predictor of the primary end point (HR 3.05, 95%CI: 1.17-7.97, $p = .023$) after adjusting for age (per 10 year increments), sex, office SBP (per 10 mm Hg), office DBP (per 10 mm Hg), home SBP (per 10 mm Hg), home DBP (per 10 mm Hg), smoking, diabetes mellitus, and serum creatinine level. Home SBP was also an independent predictor of the primary end point in both the obese and non-obese patients (HR 1.36, 95%CI: 1.02-1.83, $p = .039$ vs. HR 1.36, 95%CI: 1.07-1.73, $p = .012$).

4 | DISCUSSION

The results of our retrospective analyses of 3586 patients demonstrated that AF was an independent predictor of cardiovascular events in obese patients after adjusting for home SBP in a Japanese

general practice-based cohort study. In contrast, among the non-obese patients, there was no significant difference in prognosis between the patients with sinus rhythm and those with AF. Our results showed that an elevation in home SBP posed a risk of cardiovascular events in both obese and non-obese patients, independent of the risk presented by AF.

In this general practice-based cohort study, AF was an independent predictor of cardiovascular events in patients with obesity after adjusting for covariates including age, sex, office SBP, home SBP, smoking, diabetes mellitus, and creatinine level. However, AF was not shown to present a risk of cardiovascular events in the non-obese patients. Obesity poses risks for hypertension, cardiovascular diseases such as coronary heart disease (CHD), heart failure (HF), and especially for ischemic stroke, and obesity is associated with high overall mortality.²²⁻²⁴ Obesity and overweight increase the incident risk of AF.⁹⁻¹²

Obesity and AF are, respectively, independent risks for cardiovascular events. In the Olmsted County study of a community-based cohort, HF was a risk for incident AF, and the presence of HF regardless of a preserved or reduced ejection fraction (EF) in individuals with AF was associated with all-cause mortality and cardiovascular events.²⁵ However, that study did not evaluate its population divided into patients with/without obesity.

The presence of the "obesity paradox" is known to result in a better prognosis for obesity compared to non-obesity regarding cardiovascular events in debilitating diseases such as HF and chronic obstructive pulmonary disease and in elderly patients. The existence of the obesity paradox in patients with AF has been controversial. Obesity increases the risk of the development of AF, but obesity and overweight patients with AF seem to have a better prognosis (including regarding CVD) and all-cause survival compared to normal-weight patients with AF.²⁶⁻²⁸ In a recent report

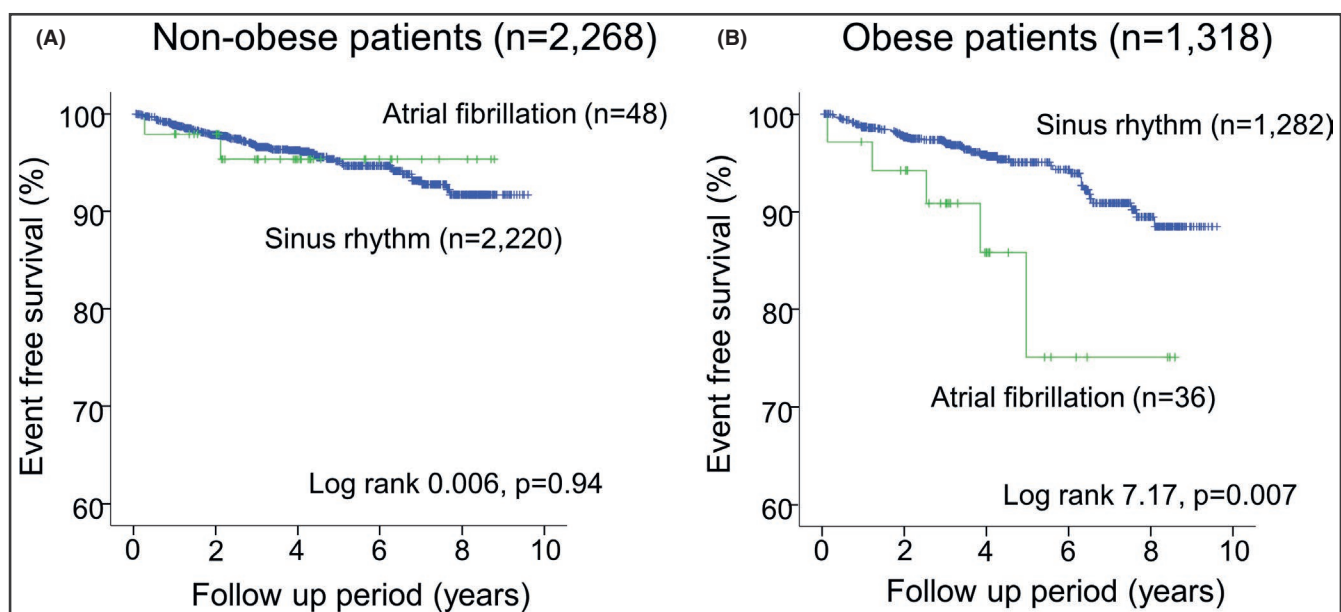


FIGURE 1 Kaplan-Meier curves for the primary end point in the (A) non-obese patients and (B) obese patients

TABLE 2 Hazard ratios for cardiovascular events

	Non-obese				Obese			
	Unadjusted hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value	Unadjusted hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
Age, per 10 years old	2.01 (1.66-2.50)	<.001	1.68 (1.27-2.24)	<.001	1.59 (1.27-1.98)	<.001	1.45 (1.05-2.01)	.026
Male	2.58 (1.73-3.85)	<.001	2.84 (1.72-4.67)	<.001	1.22 (0.79-1.89)	.37	1.40 (0.84-2.34)	.20
Office SBP, per 10mmHg	1.09 (0.97-1.21)	.15	0.93 (0.75-1.15)	.50	1.15 (1.01-1.31)	.037	0.85 (0.65-1.12)	.24
Office DBP, per 10mmHg	0.70 (0.59-0.84)	<.001	0.90 (0.58-1.41)	.65	0.79 (0.64-0.98)	.033	1.11 (0.66-1.87)	.70
Home SBP, per 10mmHg	1.35 (1.20-1.52)	<.001	1.36 (1.07-1.73)	.012	1.30 (1.14-1.48)	<.001	1.36 (1.02-1.83)	.039
Home DBP, per 10mmHg	0.81 (0.65-0.99)	.049	0.84 (0.51-1.39)	.49	0.81 (0.64-1.03)	.90	0.78 (0.44-1.36)	.38
Smoking	0.84 (0.46-1.52)	.84	0.69 (0.34-1.40)	.30	0.55 (0.22-1.36)	.20	0.52 (0.18-1.47)	.22
Diabetes mellitus	1.66 (1.09-2.53)	.019	1.26 (0.77-2.07)	.37	3.11 (2.01-4.80)	<.001	2.45 (1.46-4.11)	.001
Creatinine, per 1 mg/dl	2.63 (1.90-3.65)	<.001	1.45 (0.79-2.68)	.23	1.60 (1.12-2.26)	.009	1.45 (0.86-2.43)	.16
Atrial fibrillation	1.06 (0.26-4.30)	.94	0.78 (0.19-3.17)	.98	3.25 (1.30-8.09)	.011	3.05 (1.17-7.97)	.023

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.

in the ORBIT-AF registry, classobese patients with AF had a 35% lower risk of all-cause mortality compared to that of normal-BMI patients.²⁹

Notably, the obesity paradox has not been observed consistently for nonfatal clinical outcomes such as stroke and HF among AF patients.²⁹⁻³¹ Even in the ORBIT-AF registry, the obesity paradox was observed concerning the end point of all-cause mortality, but it was not observed for stroke or HF.²⁹ Similarly, in the ARISTOTLE trial, obese patients with a BMI >25 kg/m² and AF had a significantly lower risk of death compared to AF patients with a normal BMI, but there was no significant a risk of stroke or systemic embolism even when the patients were divided by BMI.³¹ In a meta-analysis and systematic review of the association between BMI and adverse events in AF patients, overweight defined as BMI 25 to <30 kg/m² was associated with lower risk of all-cause mortality compared to normal BMI, whereas the incidence of stroke and systemic embolism was not significantly different between the overweight and normal-BMI patients.³⁰ In other words, the obesity paradox is not always observed in AF patients regarding of the incidence of stroke and HF. In addition, the prospective Danish Diet, Cancer, and Health study has demonstrated that obesity and overweight were risk factors for ischemic stroke, thromboembolism, or death in patients with AF, even after adjustment for CHADS2 and CHA2DS2-VASc scores.³² These previous reports are consistent with our present findings that obese patients with AF have more events such as HF and atherosclerotic cerebral infarction, and obesity worsens the prognosis of AF.

The pathophysiological mechanisms linking obesity and AF are highly complex and not well understood. The change of

hemodynamics, inflammatory responses, neurohormonal activity, and autonomic has been reported in obesity.^{33,34} Those factors may affect the prognosis of obese AF patients. Recent studies have reported an association between cardiorespiratory fitness (CRF) and risk of AF in the general population. In the CARDIOFIT study,³⁵ the authors demonstrated that improvement in CRF during long-term follow-up was associated with significantly lower burden of AF symptoms and significantly lower AF recurrence in obese individuals. CRF may be expected to improve the prognosis of obesity and AF in Japanese patients with cardiovascular risks.

In our present analyses, home SBP elevation was shown to associate with a risk of cardiovascular events in both the obese and non-obese patients. The hazard ratio representing the risk of cardiovascular events with an increase in home SBP of 10 mmHg was 1.36, which was identical in the obese and non-obese patients. In the obese patients, home SBP elevation was a predictor of cardiovascular events, independent of the risk of AF. Regardless of the presence or absence of obesity, the active assessment of home blood pressure and lowering home blood pressure will be important toward the suppression of cardiovascular events.^{36,37}

This study has several limitations. It was an observational, cross-sectional study, and thus the results do not allow us to determine the causal relationship. The number of cardiovascular events and the prevalence of AF were low. Thus, the finding that there was no significant difference in the prognosis of non-obese patients between those with sinus rhythm and those with AF may have been due to the low number of cardiovascular events. In addition, this study has too little power to debate "the obesity paradox." Further large-scale prospective studies are needed to clarify the association between obesity

with AF and cardiovascular events. In addition, AF was assessed by ECG only at baseline. Although it is likely that our population included patients with paroxysmal AF, we could not detect this type of AF. Finally, there are no available data of catheter ablation or the use of non-vitamin K antagonist direct oral anticoagulants.

5 | CONCLUSIONS

Atrial fibrillation was an independent predictor of cardiovascular events in obese patients after adjusting for home blood pressure. Further large-scale studies including various ethnic groups will be needed to assess the association between obesity with AF and cardiovascular events.

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CONFLICT OF INTEREST

K. Kario has received research grants from Omron Healthcare and A&D Co. The other authors have no conflict of interest to declare.

AUTHORS CONTRIBUTION

Kario K takes primary responsibility for this paper. Watanabe H wrote the manuscript and did the statistical analysis. Kario K, Kabutoya T, and Hoshide S collected the patients' data. Kario K acquired research grants for the J-HOP study. Watanabe H, Kabutoya T, Hoshide S, and Kario K reviewed/edited the manuscript.

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