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## Diurnal incidence of acute myocardial infarction in a Japanese population (From the Takashima AMI Registry, 1988–2004)

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### KEYWORDS

Acute myocardial infarction (AMI);  
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Registry

### Summary

**Background:** We examined the circadian periodicity of acute myocardial infarction (AMI) onset to identify any existing specific pattern using 17-year AMI registration data.

**Methods:** Data were obtained from the Takashima AMI Registry, which covered a stable population of approximately 55,000 in Takashima County in central Japan. Out of 429 registered first-ever AMI events from 1988–2004, there were 352 events with classifiable onset time. AMI onset was categorized as occurring at night (midnight to 6 a.m.), morning (6 a.m. to noon), afternoon (noon to 6 p.m.) or evening (6 p.m. to midnight).

**Results:** There was a significant diurnal variation in AMI incidence ( $P < 0.001$ ) with the highest proportion in the morning (32.4%, 95% CI: 27.7–37.5) and lowest in the nighttime (17.4%, 95% CI: 13.7–21.7). An excess AMI incidence in the morning was observed in both genders and in subjects  $\geq 65$  years old. A second surge was also observed during the later part of the day.

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The morning excess of AMI incidence was similar across seasons and days of the week. For all AMIs, the age and gender adjusted risk was 1.82 (95% CI: 1.33–2.49) times higher in the morning than at night.

*Conclusion:* A diurnal pattern of AMI onset was observed in a Japanese population with a morning peak and nighttime trough, and the pattern was similar across seasons of the year and days of the week.

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## Introduction

A circadian variation of acute cardiovascular events has been reported in various parts of the world [1–13]. Studies have reported that the onset of acute myocardial infarction (AMI) peaks in the morning hours and there is a nadir during the night period [1–9]. The data to date concerning the temporal rhythm of AMI onset are mainly from Western and European populations [1–8]. Few studies in Japan have reported the circadian variation in the incidence of AMI, but these studies were performed primarily using hospital based case series [10–13]. In contrast, there is no information on the circadian variation in AMI from any community-based population in Japan. Moreover, little is known regarding the effect of seasonality or day of the week on the circadian variation of AMI onset.

In the present study, we used an AMI registry system that covered an entire community-based population to explore whether there is a period during 24 h of the day with excess risk of AMI. We examined whether the circadian pattern was different across genders, and age-groups. We also determined other chronological factors that influence the risk of AMI, such as onset day of the week or season of the year would modify the circadian variation in AMI onset.

## Populations and methods

The Takashima AMI Registry is an integrated part of the Takashima Cardio-cerebrovascular Disease Registration system [14,15], which was established in 1988 in Takashima County, Shiga, Japan. The objective of this AMI registry was to measure trends in the incidence and case-fatality of AMI and to compare these to sources both inside and outside of Japan [14]. The population of Takashima County was 55,451 (men 49.2% and women 50.7%) in the year 2000 [16]. With an aging populace, 22.3% of the Takashima population is  $\geq 65$  years of age and this is higher than what has been reported (17.4%) for the general Japanese population [16].

Methods of case identification, classification and registration procedures, diagnostic criteria, and items of registration and data quality control are described in detail elsewhere [14,15]. For possible inclusion in the registry, all suspected AMI events, both hospitalized cases and out-of-hospital cases were identified, evaluated, and confirmed using several sources of information. For hospitalized cases, hospital admission, discharge or death records were routinely collected for suspected AMI events and validated by project criteria [17]. For non-hospitalized cases (deaths in emergency rooms, deaths on/during arrival at hospital, or community deaths) the event information was collected from emergency room records, ambulance records, and

death certificates. For information on pre-hospital fatal cases, ambulance records and death certificates at the local government were screened for acute events and validated according to the project criteria [17]. All records were cross-checked by research physicians, cardiologists and epidemiologists to verify that all eligibility criteria were satisfied before a case was included in the registry. Patient's privacy was protected at all times. This study was approved by the Institutional Review Boards of the Shiga University of Medical Science.

The AMI diagnostic criteria employed in this study were established by the Monitoring system for Cardiovascular Disease commissioned by Ministry of Health and Welfare, Japan [17]. These criteria were in accord with the World Health Organization-Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA) project [18]. Evaluation of registered events was based on medical history, clinical symptoms, electrocardiographic (ECG) findings as well as cardiac enzymes levels. For cases of out-of-hospital cardiac death, ECG findings and cardiac enzymes levels were often not available. In such cases, we had to base registration on the patients' location and symptoms at onset and their history of coronary heart disease (CHD). This information was also cross-checked by death certificates. Only first-ever definite and possible AMIs was considered in this study. An event was recorded as first-ever if the medical records for the current events had one of the followings: the patient has no previous history of AMI and the patient has never had symptoms like those of the present events more than 28 days before the onset. Items recorded at registration of an AMI were the date and time of the event, the situation and symptoms at the time of the event, clinical observations at the event, past and family history, smoking history, drinking history, rehabilitation, fatality (within 28 days), cause of death, etc.

## Analysis parameters and statistical methods

Our analysis included all patients from the Takashima AMI Registry who suffered their first ever AMI irrespective of outcome. The present study covered the time period from the 1st of January, 1988 to the 31st of December, 2004.

Assuming that AMI onset is not related to the time of day, then the time of AMI onset would be evenly distributed throughout the day. To investigate the daily distribution of AMI, the frequency of observed cases was determined in each one-hour interval for 24 h, and was compared with the expected frequency using a  $\chi^2$  test for a single population (for goodness of fit to the null model of equal distribution of AMI). For "wake-up AMI" (symptoms first recognized at awakening) and AMI of "unknown onset status"

(no information on status at onset), the time of awakening or symptom recognition was used as the time of onset. We performed a sensitivity analysis assuming different scenarios regarding the onset time of these AMIs. First, the distinction was ignored and the data were analyzed without regard to onset status. Second, the data were analyzed omitting "wake-up AMI" and "unknown onset status" AMI. Third, we assumed that symptoms present on awakening or unknown status at onset indicated an AMI occurring at times distributed evenly over the preceding 8 h, the onset times of these AMIs were redistributed evenly across the 8 h preceding the reported onset time. The results of all these approaches described above showed a similar pattern and significant distribution of AMI onset across the hours of the day. Based on this observation, the reported AMI onset time was used as a surrogate for the onset time for patients with "unknown onset status" or "wake-up-AMI" in further analyzes.

Each AMI event was categorized as occurring in the nighttime (midnight to 6 a.m.), morning (6 a.m. to noon), afternoon (noon to 6 p.m.) or evening (6 p.m. to midnight) based on its time of onset. To examine the effect of age on the pattern of AMI incidence, patients were stratified into <65 and ≥65 years old at the time of AMI onset. The proportions of AMIs that occurred during each 6-h time block were determined for each gender and age group. Confidence intervals (CI) for proportions were calculated by Wilson's method [19].

Poisson regression analysis was used to calculate the incidence rate ratio of AMI and the corresponding 95% CI adjusted for age and gender for morning, afternoon and evening, with nighttime serving as the reference.

All statistical analyses were performed using SPSS® for windows, version 17.0 (SPSS Inc., Chicago, Ill.) and SAS® version 9.1 (SAS Institute, Cary, NC).

## Results

There were 429 first-ever AMI events during the study period of 1988–2004. Table 1 shows the demographic characteristics of the populations of the catchment area of the Takashima AMI Registry, and summarizes the characteristics of the patients with classifiable and unclassifiable onset times. There were no significant differences in characteristics between the patients with and without classifiable onset times. Among the 352 patients (men: 230 and women: 122) with classifiable AMI onset time, the mean age was 68.0 years (SD: 13.9) for men and 75.2 years (SD: 11.3) for women.

Fig. 1 shows the frequency of AMI onset in 24 one-hour intervals. There was a clear and significant diurnal variation in AMI incidence ( $P < 0.001$ ), with the peak occurrence from 8 a.m. to 10 a.m. followed by a second surge from 6 p.m. to 8 p.m. and a trough from 11 p.m. to 4 a.m. AMI occurred when awake in 228 patients, and AMI symptoms were first noted on awakening in 61 patients. When the AMIs with unknown onset status or those occurring during sleep were redistributed throughout the preceding 8 h of the reported onset time, the significant variation persisted ( $P < 0.001$ ) with a similar periodicity.

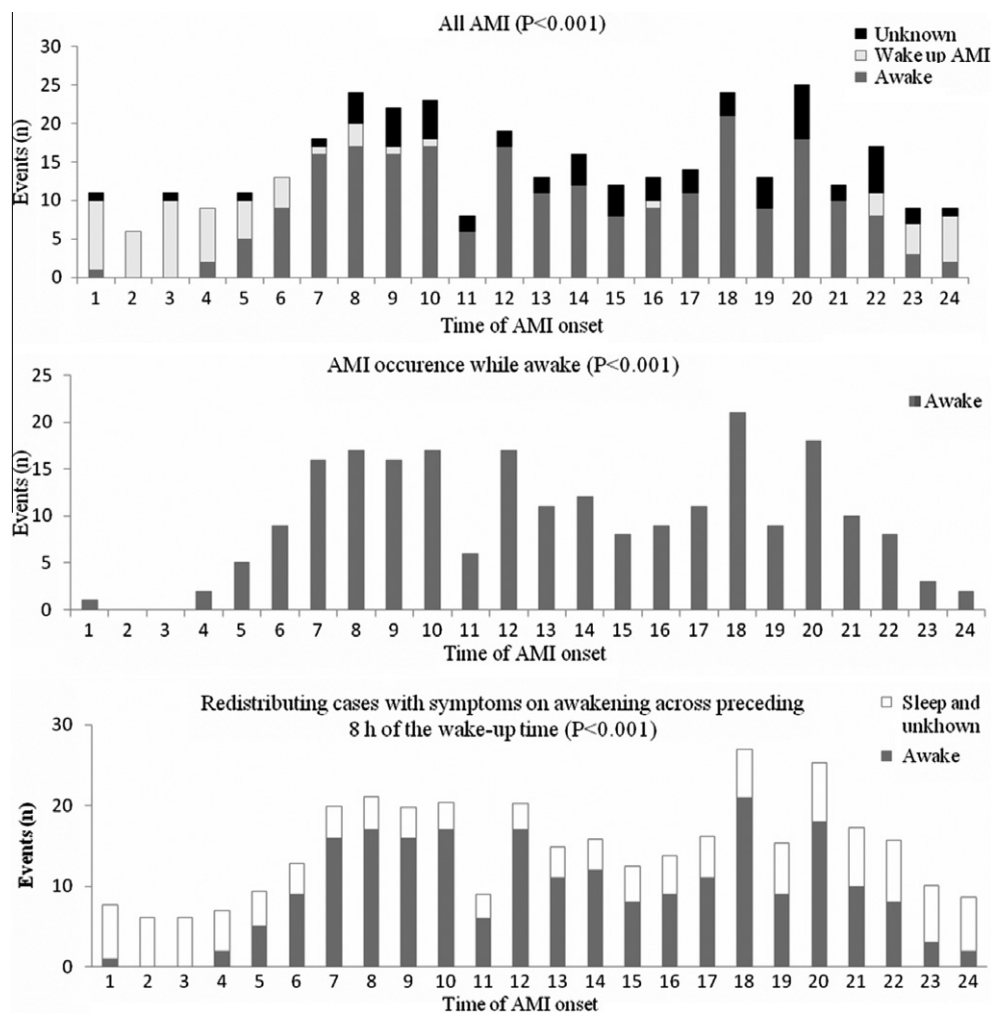
Table 2 shows the proportion of AMI incidence across the four 6-h time blocks. For all AMIs, the highest proportion occurred in the morning period (32.4%, 95% CI: 27.7–37.5) followed by the afternoon period (26.1%, 95% CI: 21.8–31.0), with the lowest proportion in the night period (17.4%,

**Table 1** Population characteristics of the catchment area and registered acute myocardial infarction patients of Takashima AMI Registry, Japan (1988–2004).

Characteristics	Takashima county population <sup>a</sup>		
Overall	55,451		
Men	27,323 (49.3%)		
Women	28,128 (50.7%)		
<65 years	43,081 (77.7%)		
≥65 years	12,354 (22.3%)		
	Registered AMI cases		
	Classifiable onset time	Unclassifiable onset time	<i>P</i>
<i>All AMI</i>			
Total incidence	352	77	
Average age at onset, years	70.5 ± 13.5	72.2 ± 12.8	0.313
<i>Gender</i>			
Men	230 (65.3%)	51 (66.2%)	
Women	122 (34.7%)	26 (33.8%)	0.881
<i>Risk factor history</i>			
Hypertension	138 (39.2%)	30 (39.0%)	0.968
Diabetes mellitus	97 (27.6%)	20 (26.0%)	0.778
Drinking	62 (17.6%)	9 (11.7%)	0.205
Smoking	66 (18.8%)	14 (18.2%)	0.908
Hypercholesterolemia	84 (23.9%)	11 (14.3%)	0.067

Comparisons between the groups were performed with 2-tailed Students's *t* test or  $\chi^2$  test.

<sup>a</sup> Based on the 2000 population census of Japan (age reported unknown for 16 persons).



**Figure 1** Bar graphs showing a sensitivity analysis for the incidence of AMI onset across the time of the day. The number of events is shown on the y axis and the hour of the day on the x axis. Three different methods were explored for incorporating ‘wake-up AMI’ (symptoms first recognized at awakening) and AMI of ‘unknown onset status’ (no information on status at onset) into the analysis of data from the Takashima AMI Registry, Shiga, Japan (1988–2004). The topmost figure shows the distribution of all AMI onsets (shaded areas, patients with onset while awake; open areas, patients with ‘wake-up AMI’; black areas, patients with ‘unknown onset status’). The second figure shows the distribution for only patients with AMI onset while awake (‘wake-up AMI’ and AMI of ‘unknown onset status’ were excluded). The bottom figure shows the results after redistributing cases with ‘wake-up AMI’ and ‘unknown onset status’ over the 8 h preceding the reported onset time (shaded areas, patients with onset while awake; open areas, patients with ‘wake-up AMI’ and ‘unknown onset status’).

95% CI: 13.7–21.7). An excess AMI incidence in the morning followed by the afternoon was observed in both men and women, and in both age groups. The proportion 7-day and 28-day fatal events were observed to have occurred in higher proportion in the morning period and lower in night period. The AMI onset showed a similar pattern, that lowest incidence occurred during night time, across seasons (spring, winter, summer, and autumn) and days of the week (weekend and weekday). Age and gender adjusted risk of AMI incidence was 1.82 (95% CI: 1.33–2.49) times higher in morning compared to the night period (Fig. 2).

## Discussion

The present study shows a diurnal variation in the incidence of AMI events in both men and women, in younger and older

age groups. We observed that a higher proportion of AMI occurred during the morning followed by a second surge during the later part of the day. When AMI were clustered within 6-h time intervals, the morning risks mimic the observation for the 24 one-hour distributions. Characterizations of the time of AMI onset have been plagued by the problem of determining time of onset of events detected when the patient awakens. The proportion of time patients spend asleep are difficult to measure. However, even if the presumed hour of onset for the wake-up AMI was distributed over the preceding 8 h, the variation was still significant. The periodicity for the AMI onset is also reflected in AMI fatality. Similar patterns were observed across seasons of the year and day of the week. In all instances the risk was lower during the night.

Our findings are consistent with other studies [1–13] from around the world on the onset time of AMI that

**Table 2** Proportion (%) of acute myocardial infarction across time blocks of the day by gender, age group, fatality, season and day of the week in the Takashima AMI Registry, Japan (1988–2004).

Characteristics	Number of cases	Time blocks <sup>a</sup>								
		Night (midnight to 6 a.m.)		Morning (6 a.m. to noon)		Afternoon (noon to 6 p.m.)		Evening (6 p.m. to midnight)		
		%	95% CI <sup>d</sup>	%	95% CI	%	95% CI	%	95% CI	
All cases	352	17.4	(13.7–21.7)	32.4	(27.7–37.5)	26.1	(21.8–31.0)	24.1	(19.9–28.9)	
<i>Gender</i>										
Men	230	18.7	(14.1–24.3)	30.9	(25.2–37.2)	27.4	(22.0–33.5)	23.0	(18.0–29.0)	
Women	122	14.8	(9.4–22.3)	35.2	(27.2–44.2)	23.8	(16.9–32.2)	26.2	(19.1–34.8)	
<i>Age group</i>										
<65 years	103	22.3	(15.2–31.5)	26.2	(18.5–35.6)	27.2	(19.3–36.7)	24.3	(16.8–33.6)	
≥65 years	249	15.3	(11.3–20.3)	34.9	(29.2–41.1)	25.7	(20.6–31.5)	24.1	(19.2–29.8)	
<i>Fatal AMI</i>										
7-day fatal cases	123	15.4	(9.9–23.0)	33.3	(25.5–42.2)	25.2	(18.2–33.7)	26.0	(18.9–34.6)	
28-day fatal cases	132	14.4	(9.3–21.5)	35.6	(27.8–44.2)	25.0	(18.3–33.2)	25.0	(18.3–33.2)	
<i>Seasons of the year<sup>b</sup></i>										
Winter AMI	105	14.3	(8.6–22.5)	39.0	(30.1–48.8)	21.0	(14.1–29.9)	25.7	(18.1–35.0)	
Spring AMI	102	23.5	(16.2–32.8)	28.4	(20.4–38.0)	25.5	(17.8–34.9)	22.5	(15.3–31.8)	
Summer AMI	71	19.7	(11.8–30.8)	29.6	(19.9–41.3)	25.4	(16.4–36.9)	25.4	(16.4–36.9)	
Autumn AMI	74	10.8	(5.2–20.3)	31.1	(21.4–42.6)	35.1	(25.0–46.8)	23.0	(14.6–34.1)	
<i>Days of the week<sup>c</sup></i>										
Weekend AMI	113	18.6	(12.3–26.9)	40.7	(32.0–50.1)	21.2	(14.5–29.8)	19.5	(13.0–27.9)	
Weekday AMI	239	16.7	(12.5–22.1)	28.5	(23.1–34.5)	28.5	(23.1–34.5)	26.4	(21.1–32.3)	

<sup>a</sup> Morning (6 a.m. to noon), afternoon (noon to 6 p.m.), evening (6 p.m. to midnight), and night (midnight to 6 a.m.).

<sup>b</sup> Winter (December, January and February), spring (March, April and May), summer (June, July and August), and autumn (September, October and November).

<sup>c</sup> Weekend (Saturday and Sunday) and weekday (Monday to Friday).

<sup>d</sup> CI, confidence interval.

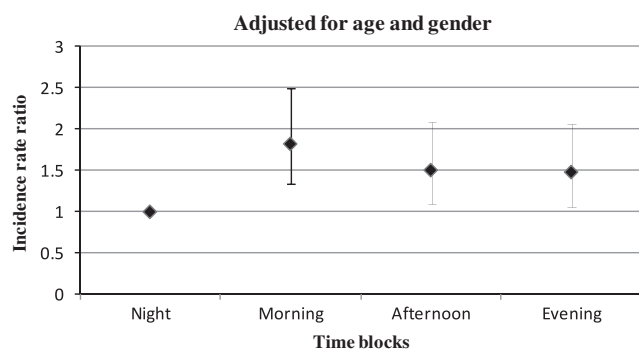
reported a morning peak from 6 a.m. to noon. Similar to our observations, an additional evening surge from 6 p.m. to 10 p.m. was also reported in some studies [3,5,8,10,12,13]. Tanaka et al. analyzing a comparable sample size to ours, studied hospital based case series of 336 AMI patients between 1988 and 1993 [20]. In their study, they observed a morning peak for AMI onset (34.8% AMI onset) with a second peak (23.8% AMI onset) during evening. However, studies based on hospital admission case series are in risk of referral bias and may not account for all events in a community.

In our study population, the observed morning peak was even more prominent during the weekend as well as during the winter. Weekends [21] as well as colder seasons [22] have been reported to be high-risk periods for cardiovascular events. The combined effect of morning high risk with these two periods might have been reflected in our findings. These observations point towards the influence of internal or external triggering factors in both the activities of daily living which varies across days of the week as well as effect of environmental factors which varies across season of the years. The identity of these triggering factors requires further exploration. Since the present study was based on a registry data, it was not possible to explore the mechanisms responsible for the circadian variation in AMI incidence. Changes in the rest/activity cycle with a shift from the

nonworking night to the active morning might serve as a trigger for AMI. The physiological processes related to a change in these activities may trigger AMI. An interesting area for future investigation will be to determine the relationship between AMI occurrence and variations in physical activity and daily routines across hours of the day using longitudinal data.

Although the mechanisms underlying the diurnal variation of AMI are not yet fully understood, the probable contributors include the observed day/night rhythmicity in physiological factors such as blood pressure [23], platelets aggregability [24], fibrinolytic activity [25], and serum concentrations of catecholamine or cortisol [26,27]. The reported morning blood pressure surge corresponds temporally with the higher incidence of AMI in the morning. Furthermore, physical activity has also been shown to have a diurnal variation [28]. Increased physical activity is regarded as the major determinant of the morning surge in blood pressure, which might also increase the risk of AMI [28]. The abrupt shift from no physical activity during sleep to sudden physical activity on awakening could serve as a trigger for AMI. In addition to a morning surge in AMI incidence, we also observed an evening peak in AMI incidence. It has been hypothesized that this secondary surge may be related to ingestion of the evening meal [29] or postprandial physical activity [30].





**Figure 2** The age- and gender-adjusted incidence rate ratios and 95% CIs are shown for the occurrence of AMI in the morning (6 a.m. to noon), afternoon (noon to 6 p.m.), and evening (6 p.m. to midnight) compared with the night (midnight to 6 a.m.). Takashima AMI Registry, Shiga, Japan (1988–2004).

Our registry system was designed to capture all the cases in the study area by covering all hospitals in the county. It has been estimated that more than 98% of hospital admissions of Takashima County residents are seen in these institutions [31]. To ensure that eligible patients hospitalized outside the county were included; registration procedures were also conducted at three high-level medical facilities outside the county. County ambulance records were also checked for this purpose. Even for referral cases to other hospitals, almost all the patients in the county are first taken to one of the local hospitals by ambulance before transfer. Therefore, in our registration system, registration of AMI cases in the study area was almost complete. In Japan, almost 100% of the residents are covered by health insurances under the control of Ministry of Health and Welfare [32]. Health insurance is not expensive and the policies cover all diseases, except for injuries due to traffic accidents since they are covered by mandatory automobile insurance. Therefore, the usual practice in Japan is for individuals with health problems to visit general physicians in the community, who consistently refer patients with suspected AMI to secondary- or tertiary-level hospitals for more extensive investigations. In addition, 24-h emergency ambulance service is available for residents without charge. The common practice in Japan is to take patients with any acute disease condition to an emergency facility. Thus, we believe that very few patients were omitted from our registration system.

Similar to most other studies, the main limitation of the current report was missing information on the onset time for some of the registered events because we relied on patient chart review to obtain all data used. We analyzed the AMI events excluding the cases with missing information on the time of onset. Additionally, the Takashima AMI Registry covers a rural and semi-urban population in Japan that may have been different from the metropolitan population.

In conclusion, we found that there was a chronological pattern of increased AMI incidence during morning hours. This increased risk persisted after adjustment for age and gender. Our analysis points towards an influence of internal or external trigger factors in the time preceding the acute

onset of AMI. The identification of these trigger factors, which may be of significant use in cardiovascular disease prevention, requires further investigation.

## Conflict of interest statement

No conflict of interest.

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