Admission During Off-Hours Does Not Affect Long-Term Clinical Outcomes of Japanese Patients with Acute Myocardial Infarction

J-MINUET Substudy

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on behalf of J-MINUET investigators

Summary

Discordant results have been reported on outcomes of acute myocardial infarction (AMI) patients who present during off-hours.

We investigated 3283 consecutive patients with AMI who were selected from the prospective, nationwide, multicenter registry (J-MINUET) database comprising 28 institutions in Japan between July 2012 and March 2014 to determine the current impact of off-hours presentation (defined as weekends, holidays, and weekdays from 8:01 PM to 7:59 AM) at hospitals on long-term clinical outcomes. The primary endpoint was a composite of all-cause death, non-fatal MI, non-fatal stroke, cardiac failure, and urgent revascularization for unstable angina for up to 3 years from the index event.

During off-hours, 52% of patients presented. Primary percutaneous coronary intervention was performed in 85% of patients, and the door-to-balloon time was comparable between off-hours and regular hours (74, interquartile range [IQR] 52 to 113 versus 75, IQR 52 to 126 minutes, $P = 0.34$). Rate of overall primary endpoint overall did not overall significantly differ (25.3% versus 23.5%, log-rank $P = 0.26$), in patients with ST-elevation myocardial infarction (STEMI) (log-rank $P = 0.93$) and in patients with non-ST-elevation myocardial infarction (NSTEMI) (log-rank $P = 0.14$). Multivariate Cox regression analysis showed that off-hours presentation was not significantly associated with long-term clinical events in all cohorts.

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The impact of presentation during off-hours or regular hours on the long-term clinical outcomes of Japanese patients with AMI is comparable in contemporary practice.

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Key words: Coronary artery disease, Off-hour presentation, Outcome measurements

Acute myocardial infarction (AMI) remains a leading cause of mortality and morbidity worldwide.¹⁾ Percutaneous coronary intervention (PCI) is an established revascularization therapy for patients with AMI²⁾ but still challenging in the high-risk AMI population.^{3,4)} Mortality rates are reportedly higher among patients with AMI who are admitted during off-hours (nights, weekends, and holidays) than those admitted during regular hours.⁵⁻⁸⁾ In contrast, an equal number of conflicting results have been reported,⁹⁻¹²⁾ which raises the question as to whether the quality of care and clinical outcomes differ depending on the time of admission to hospital.^{13,14)} We previously found no significant differences in short-term (in-hospital) clinical outcomes between regular hours and off-hours.¹⁵⁾ In this study, most patients (85%) were treated with PCI. Various factors during off-hours such as availability of cardiologists, support staff for the cardiac catheterization, the number of skilled nursing staff, and human factors such as sleep deprivation and fatigue may attribute to the PCI-related late events. Thereafter, we conducted a *post hoc* analysis of the J-MINUET study to evaluate associations between off-hours presentation and long-term clinical outcomes in patients with AMI in contemporary practice in Japan.

Methods

Study participants: The multicenter, prospective, observational J-MINUET (Japan Registry of Acute Myocardial Infarction Diagnosed by Universal Definition) study enrolled consecutive patients with AMI who presented at 28 Japanese medical institutions between July 2012 and March 2014.¹⁶⁾ The diagnosis of AMI was based on the ESC/ACC Foundation (ACCF)/American Heart Association (AHA)/World Heart Federation Task Force for the Universal Definition Myocardial infarction.¹⁷⁾ Only type 1 (spontaneous MI related to ischemia due to primary coronary events) and type 2 (MI secondary to ischemia due to either increased oxygen demand or decreased supply) were included in this study. The baseline demographic and clinical characteristics of 3283 patients with AMI were evaluated. ST-elevation myocardial infarction (STEMI) was diagnosed in the presence of new ST elevation at the J point in at least two contiguous leads. New or presumably new left bundle branch block was considered equivalent to STEMI. This study proceeded according to the Declaration of Helsinki with the approval of the ethics committees of every participating institution.

Outcome measurements: The primary outcome was a composite of all-cause death, non-fatal MI, non-fatal stroke, cardiac failure, and urgent revascularization of unstable angina after the index MI for up to 3 years among patients presenting either during regular hours (defined as

weekdays from 8:00 AM to 8:00 PM) or off-hours (defined as weekends, holidays, and weekdays from 8:01 PM to 7:59 AM).¹⁸⁾ In brief, we included only types 1 and 2 non-fatal MI and defined cardiac failure as heart failure requiring hospital admission. Secondary endpoints defined (1) death; (2) composite of death and non-fatal MI; (3) death, non-fatal MI, and non-fatal stroke; and (4) composite of death, non-fatal MI, non-fatal stroke, and cardiac failure.

All patients were clinically followed up after the index MI through reviews of medical records, telephone contact, and postal-mailed questionnaires for up to 3 years.

Statistical analysis: We used information derived from the database of the J-MINUET study for this sub-analysis. Continuous variables presented as medians (25th to 75th percentiles) were compared using unpaired *t*-tests or Mann-Whitney *U*-tests. Categorical variables are expressed as numbers and ratios (%) and were compared using chi-square or Fisher's exact probability tests. Unadjusted cumulative event rates were estimated using Kaplan-Meier curves and compared between groups using log-rank tests overall and in STEMI and NSTEMI cohorts. Hazard ratios (HR) and 95% confidence intervals (CI) were determined using Cox proportional hazards models. Determinants of primary outcome were assessed using univariate and multivariate Cox regression analyses. Multivariable analyses included the established prognostic risk factors for cardiac events according to primary paper (adjusted for age, sex, hypertension, diabetes, dyslipidemia, chronic kidney disease, current smoking, previous MI, previous stroke, Killip class, type of MI, logarithm of time from onset to admission, urgent coronary angiography, primary PCI, and urgent bypass surgery).¹⁶⁾ Values with *P* < 0.05 were considered statistically significant. All data were statistically analyzed using JMP12.2 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics: Among the 3283 AMI patients in the present substudy, 52% of them were presented during off-hours (Figure 1). The baseline clinical characteristics of the patients are shown in Table I. The median age was 69 (IQR 61-78). The patients who presented during off-hours were younger and had a higher incidence of STEMI and advanced Killip class than those who presented during regular hours. The median amount of time that elapsed between symptom onset and presentation time was shorter for patients who presented during off-hours than regular hours (120, IQR 60-256 versus 215, IQR 90-610 minutes, *P* < 0.0001). Primary PCI was performed in 85% of the patients. Door-to-balloon time was comparable

Figure 1. Study flow chart.

between the groups (74, IQR 52-113 versus 75, IQR 52-126 minutes, $P = 0.34$; Figure 2). Door-to-balloon time was also comparable between patients with STEMI who presented during off-hours and regular hours (64, IQR 48-92 versus 67, IQR 50-93 minutes, $P = 0.34$; Figure 3).

Clinical outcomes: Rates of major cardiovascular events during 3 years of follow up were comparable overall and in STEMI and NSTEMI (25.3% versus 23.5%, log-rank $P = 0.26$; 23.0% versus 21.2%, log-rank $P = 0.93$ and 31.4% versus 27.7%, log-rank $P = 0.14$, respectively; Figure 4). Kaplan-Meier curves of secondary endpoints are shown in Figure 5. In multivariate Cox regression analysis, off-hour presentation was not significantly associated with the long-term adverse clinical outcomes overall and in STEMI and NSTEMI cohorts (HR, 1.03, 95% CI 0.87-1.21, $P = 0.26$; HR 1.01, 95% CI 0.82-1.23, $P = 0.93$; HR 1.10, 95% CI 0.84-1.44, $P = 0.47$, respectively; Table II).

Discussion

We analyzed 3283 patients with AMI from the prospective, nationwide, multicenter registry in Japan (J-MINUET). We found that long-term prognosis was comparable for both patients with AMI who presented during both regular hours and off-hours and that presenting during off-hours was not significantly associated with long-term outcomes after adjusting for risk factors.

Previous studies have shown that short-term mortality rates among patients with AMI are worse if they present to hospitals during off-hours compared with regular hours.⁵⁻⁸ Several proposed explanations include a lower likelihood of receiving evidence-based treatment or timely reperfusion therapies,¹⁹ variations in healthcare delivery between daytime and nighttime, fewer hospital staff during nighttime, and staff level of expertise.^{20,21} In contrast, a few number of studies have found an association between off-hours presentation and outcomes: long-term adverse clinical outcomes were worse among patient admitted during off-hours compared with during regular hours.^{22,23} In contrast, recent studies have found no differences in long-term outcomes of patients with AMI regardless of the time of presentation and our results are com-

patible with these studies.²⁴⁻²⁶ A recent report from a high-volume center in the Netherlands found that the clinical outcomes of 4352 consecutive STEMI patients between 2000 and 2009 were similar for up to 4 years after the index primary PCI.²⁴ The Swedish Coronary Angiography and Angioplasty Registry study of 7136 patients with STEMI who underwent primary PCI between 2004 and 2013 found similar long-term prognoses during regular-hours and off-hours presentation.²⁵ Cubeddu *et al.* reported similar short- and long-term clinical outcomes for patients in the prospective cohort database of the A Harmonizing Outcomes With Revascularization and Stents in AMI (HORIZONS-AMI) study.²⁶ Our findings are consistent with these recent results. The comparable outcomes between the regular-hours and off-hours admissions can be explained by overall improvements in STEMI programs and better-quality performance regardless of the time of presentation.

Previous studies have identified delays in door-to-balloon time during off-hours^{27,28} and a meta-analysis found longer door-to-balloon time and worse clinical outcomes for patients who presented during off-hours than during regular hours.⁸ A recent prospective multicenter cohort study showed an almost linear relationship between contact-to-balloon times and mortality in patients with STEMI treated within 60-180 minutes of the first medical contact.²⁹ Dasari *et al.* described an average delay in door-to-balloon time of 16 minutes when patients present off-hours.³⁰ We found here that the door-to-balloon time among patients requiring primary PCI was comparable between regular-hours and off-hours presentation, indicating that primary PCI facilities in Japan offer a consistent quality of healthcare, and this might be a factor in the favorable clinical outcomes of patients who present during off-hours.

In contrast, total ischemic time has not improved recently and this correlates with increased risk of adverse outcomes.³¹ A report from CREDO Kyoto registry in Japan showed that an onset-to-balloon time less than 3 hours provides better 3 year clinical outcomes,³² suggesting that continuous effort to reduce total ischemic time is required to improve outcomes for patients with AMI. This study identified shorter transportation time in patients presented during off-hours. Several possible explanations for the inconsistent results concerning the duration of transportation have been suggested. One is that Japan has a unique healthcare system in which social health insurance offers universal healthcare unlike many other developed countries.³³ This system allows patients to call emergency medical services at any time and be taken to a hospital at no charge. Consequently, most patients with AMI in Japan are managed at centers with 24/7 primary PCI facilities. Another factor is that significantly more frequent interfacility transfer during regular hours results in longer transportation time. A report from the CREDO KYOTO registry in Japan found that interfacility transfer was associated with worse clinical outcomes for patients with STEMI undergoing primary PCI.³⁴ The higher rate of interfacility transfer during regular hours might not result in an outcome difference between regular hours and off-hours. Increased focus on prehospital management and a

Table I. Baseline Clinical Characteristics of the Study Population

	Regular-hours (<i>n</i> = 1573)	Off-hours (<i>n</i> = 1710)	<i>P</i> value
Age, years	71 (62-79)	68 (59-78)	< 0.0001
Male	74.4%	76.0%	0.31
Hypertension	68.7%	64.5%	0.0115
Diabetes	36.7%	36.0%	0.68
Dyslipidemia	52.0%	51.9%	0.94
Current smoking	31.8%	36.0%	0.0133
CKD	44.6%	44.9%	0.84
Prior MI	12.2%	12.0%	0.83
Prior PCI	15.7%	14.9%	0.55
Prior CABG	2.7%	3.1%	0.52
Prior stroke	12.2%	10.5%	0.12
Diagnosis			< 0.0001
STEMI	64.8%	72.6%	
NSTEMI	35.2%	27.4%	
Killip Classification			0.0079
Class 1	77.9%	73.5%	
Class 2	9.0%	9.5%	
Class 3	4.2%	6.5%	
Class 4	8.9%	10.5%	
Transferred by			< 0.0001
Emergency transfer	44.8%	58.2%	
Walk-in	20.2%	16.0%	
In-hospital	3.7%	2.6%	
From other hospital	30.0%	19.2%	
Unknown	4.3%	4.0%	
Onset to presentation time, minutes			
Overall	215 (90-610)	120 (60-256)	< 0.0001
NSTEMI	278 (95-780)	135 (63-309)	< 0.0001
STEMI	185 (85-503)	119 (60-239)	< 0.0001
Urgent CAG	92.7%	93.5%	0.42
Urgent Revascularization			0.07
PCI	83.9%	86.2%	
CABG	2.6%	1.6%	
None	13.6%	12.2%	
Target lesion			0.32
LAD as IRA	45.5%	43.6%	
Multivessel disease	44.0%	43.3%	0.72
Initial TIMI flow 0/1	56.8%	63.8%	< 0.0001
IABP use	15.6%	18.6%	0.0208
PCPS use	2.4%	3.5%	0.06
Procedure			
stent use	90.1%	91.0%	0.42
DES use	66.5%	60.3%	0.0016
Door to balloon time, minutes			
Overall	75 (52-126)	74 (52-113)	0.34
NSTEMI	137 (87-272)	136 (88-319)	0.33
STEMI	64 (48-92)	67 (50-93)	0.33
Final TIMI 3 flow			
Overall	92.7%	91.0%	0.11
NSTEMI	95.0%	93.0%	0.41
STEMI	91.7%	90.4%	0.32
Systolic blood pressure, mmHg	139 (118-159)	138 (117-161)	0.43
Heart rate, bpm	77 (65-90)	77 (65-90)	0.85
Low-density lipoprotein cholesterol, mg/dL	115 (92-140)	114 (88-142)	0.32
High-density lipoprotein cholesterol, mg/dL	46 (39-54)	44 (37-53)	0.0013
Triglyceride, mg/dL	95 (64-148)	97 (59-157)	0.91
Max CK, IU/L	1232 (410-2888)	1691 (627-3493)	< 0.0001
Medication at discharge			
Aspirin	95.5%	95.9%	0.65
DAPT	74.4%	76.3%	0.24
OAC	12.1%	13.1%	0.42
ACEIs	53.0%	51.7%	0.48
ARBs	27.3%	29.5%	0.18
Beta blockers	67.2%	69.5%	0.20
Statins	86.4%	87.4%	0.42

ACEI indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CABG, coronary artery bypass graft surgery; CK, creatinine kinase; CKD, chronic kidney disease; DAPT, dual antiplatelets; IABP, intra-aortic balloon pumping; LAD, left anterior descending coronary artery; NSTEMI, non-STEMI; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support; STEMI, ST-segment elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

Figure 2. Distribution of symptom onset-to-balloon time.

Figure 3. Distribution of door-to-balloon time.

system to avoid diagnostic and treatment delay might be necessary to further improve the outcomes of patients with AMI.

Limitations: This study is based on a *post hoc* analysis and thus is subject to potential influences that might have affected the results. Although the sample size was moderate, it might not have had sufficient statistical power to determine differences in outcome measurements between regular hours and off-hours. This was not a population-

based study. The participating institutions are regional centers capable of advanced medical management. Therefore, not all patients who had AMI in the region during the study period were presented. In this study, the time from onset to presentation was significantly different between groups. The delay in presentation and prehospital management are associated with multiple factors including patient background, transfer system, ischemic preconditioning, and geographic distribution of quality of health-

Figure 4. Kaplan-Meier curves of primary endpoints. **A:** Overall, **B:** STEMI, and **C:** NSTEMI.

Figure 5. Kaplan-Meier curves of secondary endpoints. **A:** Death, **B:** composite of death and non-fatal MI, **C:** death, non-fatal MI and non-fatal stroke, and **D:** composite of death, non-fatal MI, non-fatal stroke, and cardiac failure.

care, and it is difficult to identify the prognostic factors derived from uncontrolled homogeneous observational studies. Finally, this study aimed to determine differences between presentation at hospitals during regular hours and off-hours. However, the most challenging cases in patients with AMI did not undergo triage and might not have been correctly transferred during off-hours, which might have created a selection bias for enrollment.

Conclusions

The clinical impact of presentation during regular hours or off-hours on the long-term clinical outcomes of patients with AMI in Japan is comparable in contemporary practice.

Table II. Univariate and Multivariate Cox Regression Analysis for Primary Endpoint

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Versus regular-hour off-hour presentation						
Overall	1.08	0.80-1.06	0.26	1.03	0.87-1.21	0.26
STEMI	1.08	0.90-1.29	0.40	1.01	0.82-1.23	0.93
NSTEMI	1.19	0.95-1.49	0.14	1.10	0.84-1.44	0.47

HR indicates hazard ratio; and 95%CI, 95% confidential interval. Other abbreviations as Table I. Multivariate model adjusted for age, sex, hypertension, diabetes, dyslipidemia, chronic kidney disease, current smoking, prior MI, prior stroke, Killip Class, type of MI, logarithm of time from onset to admission, urgent CAG, primary PCI and urgent CABG (according to the primary paper of J-MINUET).

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Disclosure

Conflicts of interest: The authors declare that there is no conflict of interest.

Trial registration: UMIN Unique trial Number: UMIN 000010037

Appendix

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