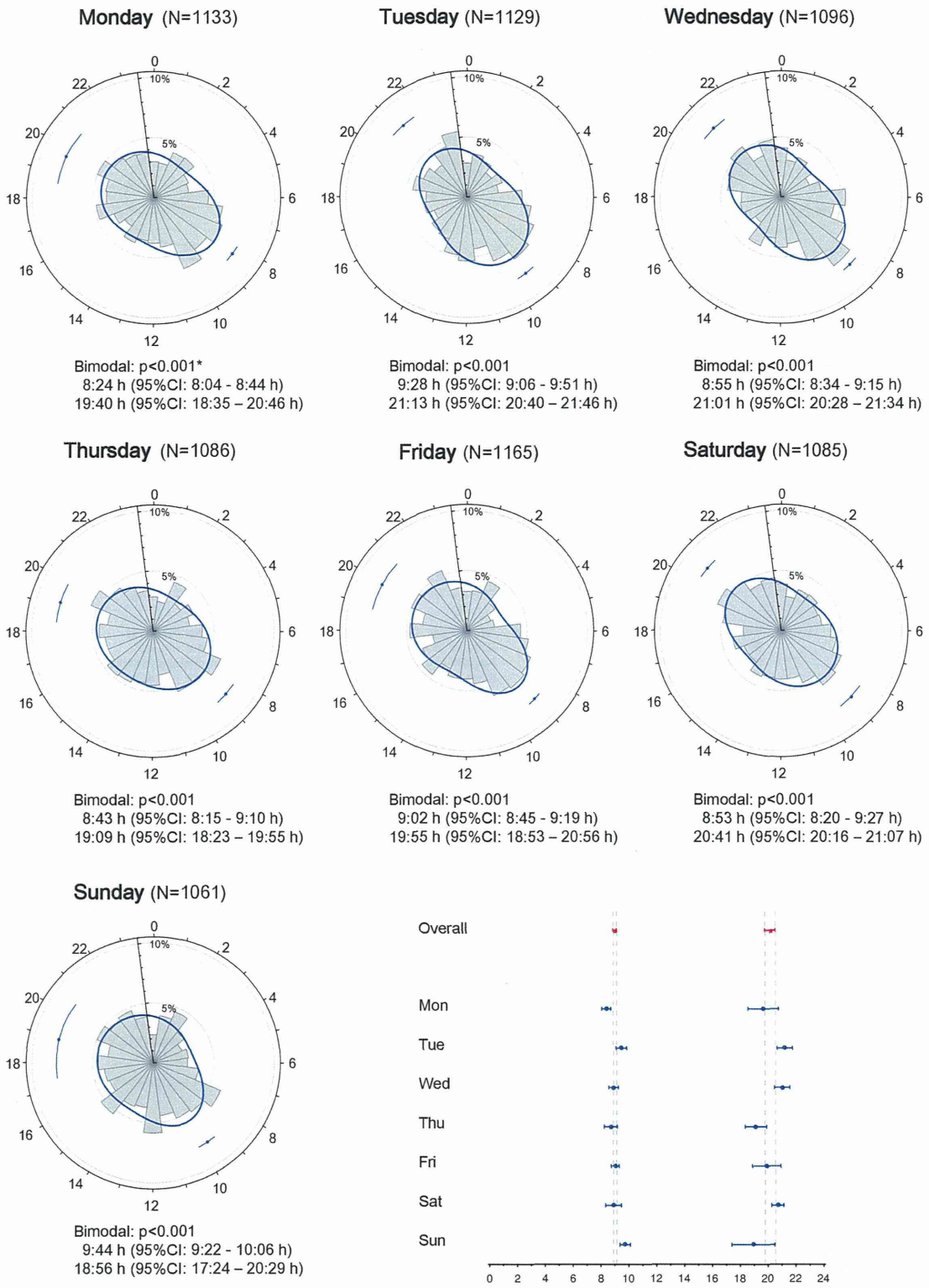


Figure 2 Circadian pattern of acute myocardial infarction (AMI) onset according to the day of the week. Circadian patterns of AMI onset based on the day of the week are shown. The estimated peak onset time and 95% CIs are shown below each circular plot. *p Values from the likelihood ratio test to examine whether the circadian pattern of AMI onset was uniform, unimodal or bimodal.

status had a statistically significant association with the circadian pattern of AMI onset, whereas several other known risk factors for AMI, including HDL and LDL cholesterol, HbA1c, hypertension, diabetes and dyslipidaemia were not related to the observed patterns (figure 3, supplementary table 1).

Among the positively associated factors, serum TG levels on admission had the greatest association with the

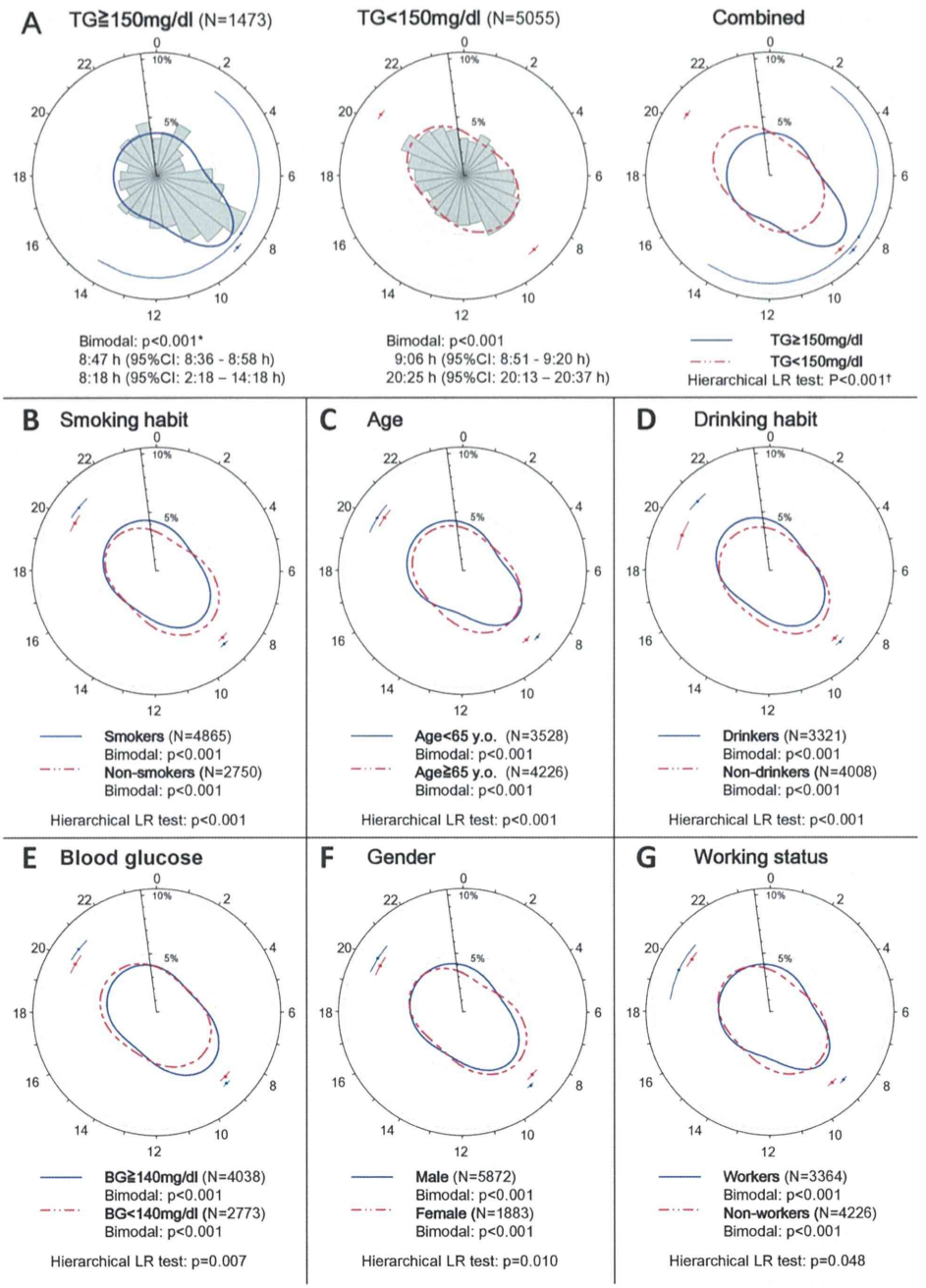


Figure 3 Circadian pattern of acute myocardial infarction (AMI) onset based on lifestyle-related factors. (A) Circular plots of the circadian pattern of AMI onset in the subpopulation with triglyceride (TG) levels ≥150 and <150 mg/dL, and the circular plot of the corresponding fitted von Mises distributions for each subgroup are shown. (B–M) Circular plots of the fitted von Mises distributions of each subgroup based on smoking habit, age, drinking habit, blood glucose levels, gender and working status, low-density lipoprotein (LDL) levels, high-density lipoprotein (HDL) levels, glycated haemoglobin (HbA1c) levels, hypertension, diabetes and dyslipidaemia. *p Values from the likelihood ratio (LR) test to examine whether the circadian pattern of AMI onset was uniform, unimodal or bimodal in each subgroup. †p Values from the hierarchical LR test to examine whether each factor affected the circadian pattern of AMI onset.

circadian pattern of AMI onset. Although the likelihood ratio test demonstrated that patients with admission serum TG levels of ≥150 mg/dL (N=1473) had two characteristic peaks during the day, the peak pattern clearly differed from the other subpopulation groups. In patients with admission serum TG levels of ≥150 mg/dL, both peaks occurred in the morning and nearly overlapped (8:18 and 8:47; figure 3A). Therefore, the subpopulation with admission TG levels ≥150 mg/dL was considered to have a high frequency of AMI onset only in the morning.

The baseline characteristics and laboratory data of patients with serum TG levels of ≥150 and <150 mg/dL

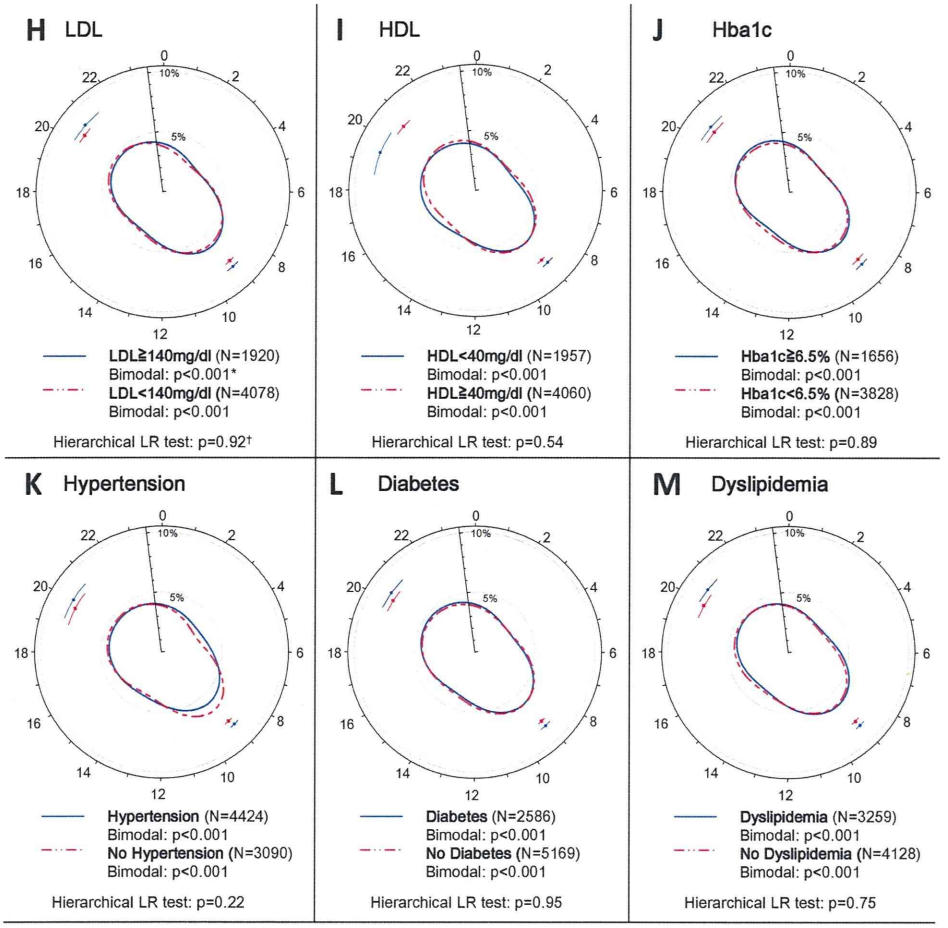


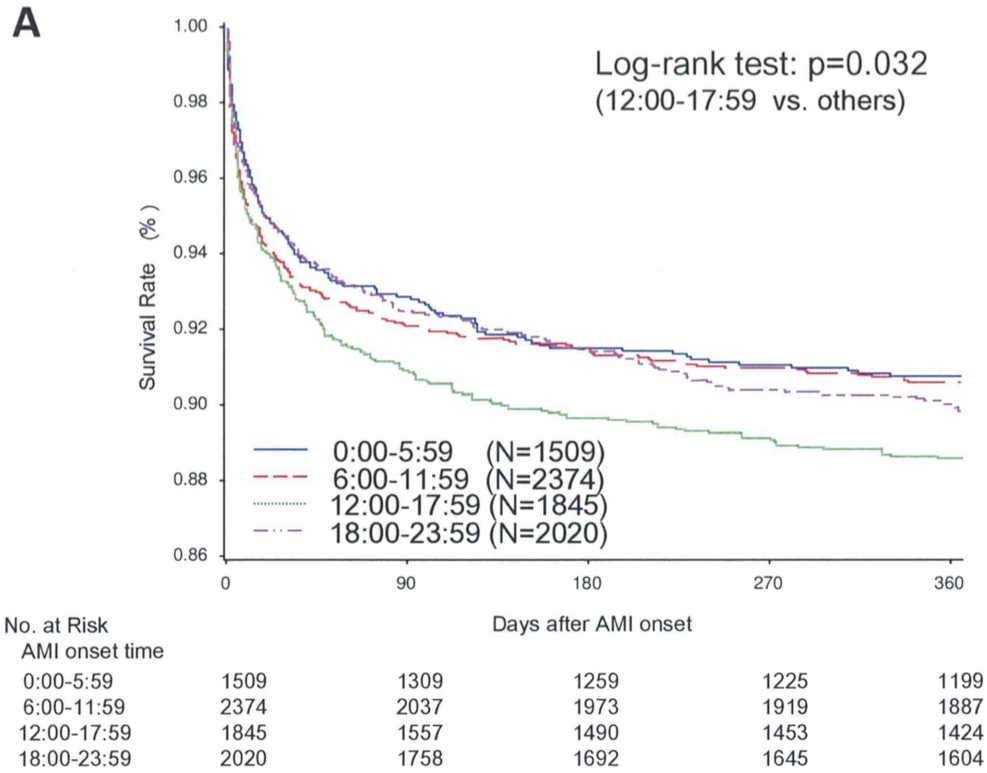
Figure 3 Continued.

on admission are shown in supplementary table 2. In the subpopulation with higher TG levels, the circadian patterns of AMI onset were characterised by a large, sharp peak in the morning from Monday to Friday, but no peaks were detected on Saturday and Sunday (bimodal: p=0.32 and 0.133, respectively; supplementary figure 1). In contrast, patients with admission serum TG levels of <150 mg/dL (N=5055) had onset peaks that occurred in the morning and evening consistently throughout the week (supplementary figure 1).

A likelihood ratio test demonstrated that all other subpopulations had two AMI onset peaks during the day: one in the morning and the other in the evening (figure 3, supplementary table 1). The subpopulations that were grouped according to smoking habit, age <65 years, male gender and active employment had a circadian pattern of AMI onset with a sharper primary peak and a less-defined sharp secondary peak compared with the other subpopulations (figure 3B, C, F, G, supplementary table 1), although the peak heights were similar between the subpopulations, with the exception of the smoker/non-smoker subpopulations. The primary AMI onset peak in the subpopulation of smokers was higher than that among non-smokers, whereas the secondary peaks were similar. Drinkers had a circadian pattern of AMI onset that was characterised by a lower and less sharp peak in the morning and a higher, sharper and later peak in the evening (9:00 (95% CI 8:48 to 9:13, 20:54 (95% CI 20:29 to 21:20)) compared with non-drinkers (9:03 (95% CI 8:53 to 9:14), 19:27 (95% CI 18:50 to 20:04); figure 3D, supplementary table 1). The subpopulation with admission blood glucose ≥140 mg/dL exhibited a circadian pattern of AMI onset with a higher and sharper primary peak and a less-defined secondary peak compared with the subpopulation of patients with AMI with blood glucose <140 mg/dL on admission (figure 3E).

One-year mortality according to onset time of AMI

One-year mortality was compared among four patient subpopulations that were grouped according to the time range of AMI onset. The baseline characteristics and laboratory data for the four groups are presented in supplementary table 3. A total of 753 deaths were recorded during a median follow-up period of 365 days. The Kaplan-Meier survival analysis demonstrated that the afternoon-onset (12:00–17:59) group had worse 1-year mortality than the other three groups (log-rank test, p=0.032; figure 4A). In the subgroup of patients with STEMI, the result was similar (log-rank test, p=0.007). The



No. at Risk AMI onset time					
0:00-5:59	1509	1309	1259	1225	1199
6:00-11:59	2374	2037	1973	1919	1887
12:00-17:59	1845	1557	1490	1453	1424
18:00-23:59	2020	1758	1692	1645	1604

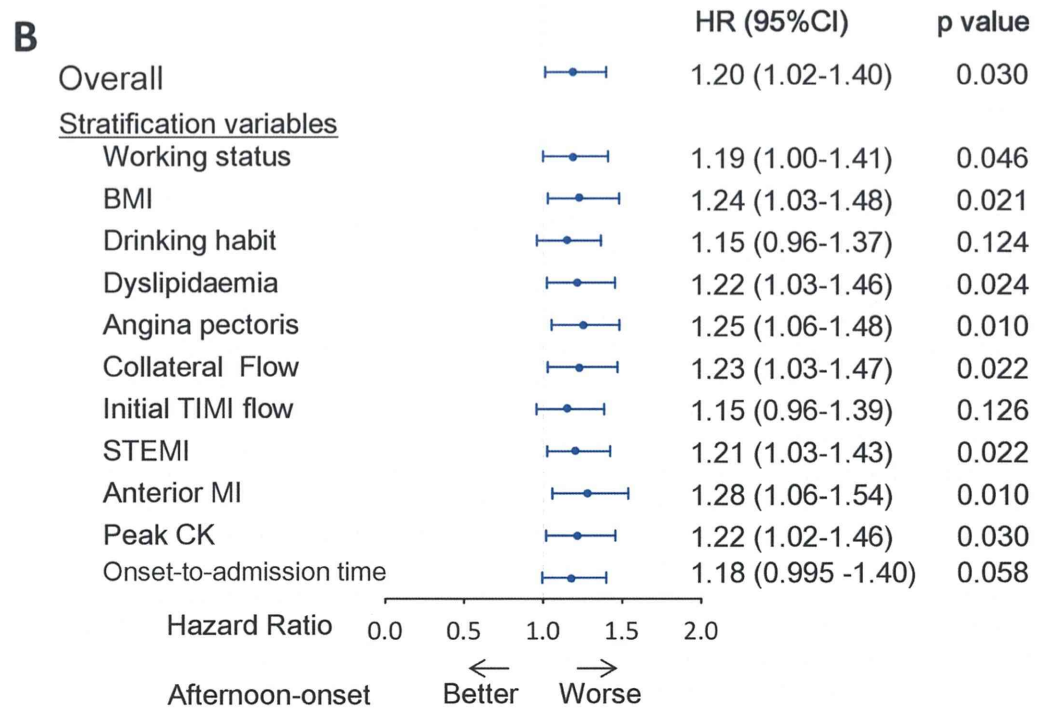


Figure 4 One-year mortality according to the onset time of AMI onset. (A) One-year mortality among the four subgroups based on AMI onset time. (B) HRs for 1-year mortality in the afternoon-onset group versus the other three onset time groups. The Kaplan-Meier survival curves of 1-year mortality among the four AMI onset time subgroups (A). A p value from the log-rank test was used to examine difference in the Kaplan-Meier curves. The HR and 95% CI, and p value for the overall population was calculated using univariable Cox regression analysis. The HRs and 95% CIs, and p values for the individual potential confounding variables were calculated using stratified Cox regression analysis, in which the variables were included into the model as stratification factors (B). AMI, acute myocardial infarction; BMI, body mass index; CK, creatine kinase; STEMI, ST-elevation MI.

univariable Cox regression analysis revealed that the HR of 1-year mortality in the afternoon-onset group as compared with the other three groups was 1.20 (95% CI 1.02 to 1.40, p=0.030, figure 4B). This result did not generally change after stratification with potential confounding factors that showed a different trend between the afternoon-onset group and the other three groups (figure 4B).

DISCUSSION

In the present study, we confirmed that AMI onset exhibits a circadian pattern characterised by bimodality, with a definite morning peak and a less-defined evening peak. Notably, several lifestyle-related factors were associated with variation in the circadian pattern of AMI onset. In particular, serum TG levels on admission for AMI were associated with a unique pattern of AMI onset that is characterised by augmented unimodal peaks on weekday mornings, suggesting that an individual's lifestyle may affect the onset pattern of AMI.

Bimodal pattern of AMI onset: morning and night-time peaks

AMI onset in our large patient cohort generally followed a circadian pattern that was characterised by a high and sharp morning peak and a lower and less-defined sharp night-time peak (figure 1), a finding that is consistent with the results of previous investigations.[1–7] Interestingly, the time of two peaks shifted in a synchronous fashion during weekdays; the secondary peaks generally occurred around 11–12 h after the morning peaks on Monday through Friday (figure 2). For example, AMI onset exhibited early morning and night-time peaks on Monday and Thursday, whereas that on Tuesday exhibited late morning and night-time peaks. Although this finding is partly consistent with the observation of Peters *et al*,[5] who reported that a secondary peak in AMI onset occurs 11–12 h after waking, the present study first demonstrated that this synchrony was present on weekdays, but absent on weekends.

Several physiological processes are considered to contribute to the bimodal pattern of AMI onset. For example, Stergiou *et al*[12] demonstrated that the two-peak diurnal variation in stroke onset occurs in parallel with variation in blood pressure, pulse rate and physical activity. Thus, the bimodality of blood pressure and heart rate[13 14] is the most likely explanation for the circadian patterns of AMI onset observed in the present study. A greater morning surge of blood pressure and heart rate[13] may explain why the night-time peak of AMI onset was lower and less-defined than the morning peak. In addition, increased blood viscosity[15] and thrombogenicity due to morning hypercoagulability[16] and hypofibrinolysis[17] also likely increased the frequency of AMI onset in the morning. It is also possible that external factors, such as physical exertion and mental stress, could be triggers for the morning onset of AMI.[18] In the present study, the younger (<65 years old), working, male and smoker subpopulations had a sharp morning peak of AMI onset compared with the elderly, non-working, female and non-smoking subpopulations (figure 3B, C, F, G). The sharpness of the morning peak might be related to increased susceptibility to physical and mental stress in these subpopulations, when they are more likely to start activities or go to work soon after waking up. Similarly, the sharp and early morning peak of AMI onset that was detected on Monday may be due to the increased physical and mental stress that is associated with the first morning of the week (figure 2). We also found that the morning peak occurred latest on Sunday (figure 2). Together, these findings strongly suggest that mental and physical activity and/or stress may act as a trigger for the morning onset of AMI.

Although many reports have examined the primary peak of AMI onset, relatively little attention has been paid to the secondary peak. We demonstrated that drinkers had a higher, sharper and later night-time peak of AMI onset than non-drinkers (figure 3D). Moreover, the night-time peak on Saturday was the highest and sharpest among the 7 days of the week (figure 2). This observation may be explained by the fact that people might likely consume alcohol and engage in social activities on Saturday night in Japan. Thus, these evening activities can result in increased sympathetic nerve activity and therefore may have contributed to the increased frequency of AMI onset at night. Taken together, our findings suggest that the morning and night-time peaks of AMI onset are influenced by physiological and socioeconomic factors.

Associations of lifestyle-related factors with the circadian patterns of AMI onset

Many previous studies on the circadian pattern of AMI onset considered gender, age, working status as potential factors affecting the circadian patterns of AMI onset.[1 4–6] We additionally incorporated laboratory data, disease and other socioeconomic factors into our analyses and found that several lifestyle-related factors, including admission serum TG and blood glucose levels, age, gender, working status and smoking and drinking habits had statistically significant associations with the circadian pattern of AMI onset. Among these factors, elevated serum TG levels (≥150 mg/dL) on admission had the largest associations with the circadian patterns of AMI onset, while the amplitude of serum TG levels on admission in patients with AMI did not have circadian variation (p=0.52; supplementary figure 2).

There are several evidences to support our findings. First, fasting hypertriglycaemia and postprandial hyperlipidaemia, which is characterised by postprandial accumulation of TG-rich lipoproteins and their partially hydrolysed products, are closely related to the development of atherosclerotic cardiovascular diseases.[19–21] Several studies have also reported that elevated serum TG levels are associated with an increased risk of MI.[22 23] Hypertriglycaemia is associated with increased

thrombogenicity,[24 25] which is reportedly associated with increased plasminogen activator inhibitor-1 (PAI-1)[26–28] and factor VII coagulant activities,[29 30] and viscosity.[31] These three factors have also been reported to affect the development of MI.[32–34] Moreover, hypertriglyceridaemia is also related to endothelium dysfunction,[35 36] which contributes to the pathogenesis of coronary artery disease.[37] In healthy participants, serum TG levels also exhibit circadian variation with a peak around 3:00.[38] Thus, it is conceivable that patients with hypertriglycaemia have further augmented TG levels and are therefore exposed to increased thrombogenicity and endothelium dysfunction in the early morning hours before dawn, which may explain the accentuated morning peak of AMI onset in patients with admission TG ≥150 mg/dL. Finally, it is reported that high plasma PAI-1 levels and excessive surges in morning blood pressure are independently and additively associated with increased risk of stroke in older patients with hypertension.[39] Thus, these lines of evidence strongly support our observation of a higher morning risk of AMI onset in the subpopulation with admission hypertriglyceridaemia.

Altered circadian patterns of AMI onset in patients with increased TG levels on admission

To the best of our knowledge, this is the first study to demonstrate an association between admission serum TG levels and the circadian patterns of AMI onset, as characterised by a lack of an evening peak in AMI onset in the subgroup of serum TG levels on admission ≥150 mg/dL compared with all other subgroups (figure 3). While LDL/HDL levels are considered to be closely associated with the development of atherosclerosis, LDL/HDL levels were not associated with onset patterns of AMI in the present study. Although the precise mechanisms for altered circadian patterns of AMI onset in patients with increased admission serum TG levels are unclear, increased serum TG might have influenced peripheral clocks residing in various tissues throughout the body, disrupting the circadian patterns of AMI onset. Indeed, recent studies have shown that energy metabolism is an important modulator of peripheral circadian clock in cardiovascular tissues.[40 41]

Our subpopulation analyses also revealed that the circadian patterns of AMI onset in patients with admission TG levels of ≥150 mg/dL had a sharp morning peak during weekdays, whereas no such peak was detected on Saturday or Sunday. This observation strongly suggests that increased thrombogenicity and endothelium dysfunction was a factor, but not the trigger, for the morning onset of AMI in our study cohort. Thus, it is conceivable that the accentuated morning peak of AMI onset in patients with admission TG ≥150 mg/dL may be due to the combination of the following three factors: (1) increased hypercoagulability, hypofibrinolysis, viscosity and endothelium dysfunction resulting from elevated serum TG levels, (2) increased risk of a morning surge of blood pressure and heart rate and (3) mental and physical stress.

One-year mortality according to AMI onset time

The association between AMI onset time and mortality is controversial. For example, Manfredini *et al*[12] reported that patients with a morning onset of AMI are characterised by higher fatal outcome, independent of site and size of infarction, while Bae *et al*[13] reported that patients with an evening-onset AMI had the worst 1-year mortality in association with poor baseline clinical characteristics. On the other hand, Holmes *et al*[14] observed no significant association between the circadian patterns of onset time and in-hospital mortality in patients with STEMI after adjusting for clinical risk factors.

In the present study, patients with an afternoon onset of AMI had the worst 1-year mortality (figure 4A). However, the baseline clinical characteristics were comparable among the four onset time groups in our study cohort. Indeed, stratification for potential confounding variables did not generally change the results, suggesting that the increased prognostic risk of AMI in the afternoon-onset group was not simply explained by differences in baseline characteristics in the present study (figure 4B). Anyway, a patient's background and physiological circadian rhythms might complexly interact with each other and affect mortality after AMI, which could lead to these different results among the studies and difficulty in interpreting the results. Further investigations are required to clarify the association of mortality after AMI and onset time.

Limitations

A few limitations of the present study warrant mention. First, this was an analysis of a prospective observational study and the results may have therefore been influenced by potential confounding factors, even after adjustment for baseline clinical and angiographic characteristics. Thus, caution is needed when interpreting the data and making generalisations to other cohorts. Second, the laboratory findings, including serum TG levels, were evaluated on admission. Therefore, we could not exclude the influence of food consumption and circadian variation of several factors, particularly serum TG levels, making interpretation of the data difficult. However, our results also demonstrated that serum TG levels were not likely the final trigger for AMI onset, as patients with TG ≥150 mg/dL on admission did not exhibit a morning peak of AMI onset on the weekend. In patients with hypertriglycaemia, hypercoagulability, hypofibrinolysis, viscosity and endothelium dysfunction are generally increased during the early morning hours before dawn,[26–31 35 36 38] resulting in enhanced susceptibility to AMI onset. Thus, under such conditions, it is conceivable that increased sympathetic activity, which was further enhanced in association with mental, physical and/or other factors, could be the final trigger for AMI onset on weekday mornings in patients with TG ≥150 mg/dL on admission. Based

on these findings, the influence of meal intake and circadian variation of serum TG levels on the morning peak of AMI onset in the population with TG ≥150 mg/dL may be minimal, if not negligible.

CONCLUSIONS

In our large cohort of consecutive patients with AMI, the circadian pattern of AMI onset exhibited bimodality and was shown to be associated with several lifestyle-related factors. Among these factors, increased serum TG levels on admission had the most marked association with circadian variation, which was characterised by an increased morning risk of AMI onset during weekdays in this subpopulation. Our findings may help to identify the underlying triggers and substrates of AMI onset and help suggest preventive measures of AMI. However, caution is warranted to interpret our results and confirmation in other cohorts is required.

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Patient consent Obtained.

Ethics approval The study protocol has been approved by the ethics committee of each participating hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

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Association of lifestyle-related factors with circadian onset patterns of acute myocardial infarction: a prospective observational study in Japan

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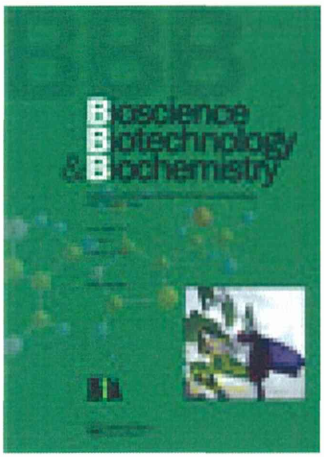

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CD36, but not GPR120, is required for efficient fatty acid utilization during endurance exercise

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