PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of Lifestyle-related Factors with Circadian Onset Patterns of Acute Myocardial Infarction: a Prospective Observational Study in Japan
AUTHORS	Edahiro, Ryuya; Sakata, Yasuhiko; Nakatani, Daisaku; Suna, Shinichiro; Usami, Masaya; Matsumoto, Sen; Hara, Masahiko; Kitamura, Tetsuhisa; Sato, Hiroshi; Yamashita, Shizuya; Nanto, Shinsuke; Hikoso, Shungo; Sakata, Yasushi; Hori, Ma; Hamasaki, Toshimitsu; Komuro, Issei

VERSION 1 - REVIEW

REVIEWER	Muller Olivier University of Lausanne
REVIEW RETURNED	24-Mar-2014

GENERAL COMMENTS	In this retrospective study based on 7755 consecutive patients with a known time of symptom onset, Ryuya Edahiro et al investigate the factors influencing circadian patterns of acute myocardial infarction onset. They observe that AMI onset exhibited bimodality and authors think that this distribution could be influenced by several lifestyle-related factors. In particular, they conclude that the subpopulation with admission TG levels ≥ 150 mg/dl was considered to have a high frequency of AMI onset in the morning. 1) A circadian distribution of TG levels is known and described. Therefore, different levels of TG levels in blood samples taken at admission could be expected, as in a population without AMI. 2) Authors should provide a figure with the circadian distribution of TG level based on hour oh symptom onset. 3) How many patients are there with TG > 150 mg/dl ? It seems that they are only a minority (Table 1 : Triglycerides (mg/dl) : 92 (58-142) 4) Authors simply show that among patients with TG levels ≥ 150 mg/dl, the morning peak is more apparent than among the overall population. Nevertheless, with the provided data, they can not conclude that (Page 12) “serum TG levels on admission (…) had a statistically significant influence on the circadian pattern of AMI onset. In fact, even patients with TG levels < 150 mg/dl have the same morning peak (see eTable 1). 5) In eTable 1, the sub-group TG ≥150 mg/dl have a second Peak earlier than the first Peak ?? Of importance, the 95% CI is 2 :18 - 14:18, which is much more importante compared to all the other 95% CI. Could the authors explain these values ? 6) In the present study, patients with an afternoon onset of AMI had the worst one-year mortality. They compare their results with Bae et

	al (Korean Circ J.2010;40:616-24), which reported that patients with evening onset AMI had the worst one-year mortality in association with poor baseline clinical caracteristics. Nevertheless, they should compare their results with other recent studies based on circadian rhythms and STEMI patients, like Holmes et al (Circ Cardiovasc Qual Outcomes. 2010;3:382-389) 7) Regarding mortality, an intepretation with the provided data is difficult in the absence of data regarding delays (JAMA. 2000;283:2941–2947 ; Time is myocardium and time is outcomes).

REVIEWER	Roberto Manfredini University of Ferrara School of Medicine Department of Medical Sciences Ferrara, Italy
REVIEW RETURNED	24-Mar-2014

GENERAL COMMENTS	The Authors aimed to investigate the possible influence the circadian pattern of acute myocardial infarction (AMI) of a series of lifestyle-related factors. The study has been performed in Japan, and is based on the data of the Osaka Acute Coronary Insufficiency Study (OACIS), and includes 7755 patients. Main significant results are the finding of a bimodality of circadian pattern of AMI onset, and a strong relationship of triglyceride (TG) levels with such pattern. I have sincerely appreciated the study, dealing with an interesting topic, and the manuscript is interesting and well written. Some considerations and suggestions will follow. **Bimodal pattern of AMI onset: morning and nighttime peaks** This aspect represents further confirmation of many studies worldwide (some of them appropriately cited in the reference section). The morning peak , as well the less pronounced evening one, have been widely reported in the literature, and also demonstrated in cerebrovascular accidents, i.e., ischemic and hemorrhagic stroke (Manfredini et al, Chronobiol Int 2005). Again, also the presence of a Monday peak is well known. Interestingly, the same morning and Monday pattern has been reported also for other non-AMI acute coronary syndromes, e.g., Tako-tsubo cardiomyopathy (Citro et al, J Am Coll Cardiol 2009; Manfredini et al, Am J Emerg Med 2010). **Impacts of lifestyle-related factors on circadian patterns of AMI onset** The impact of several major risk factors (age, sex, hypertension, diabetes, lipids) on the circadian pattern of stroke has been

	investigated several years ago both regarding the circadian variation (Casetta et al, Arch Neurol 2002), and the Monday peak (Manfredini et al, Am J Emerg Med 2008). As for the possible impact of serum TG on the circadian pattern of AMI, perhaps the general consideration of TG as a risk factor of cardiovascular disease, even if the easiest, is not fully convincing to explain a circadian interference. Again, the evaluation of a blood lipid marker in 'acute' conditions is doubtful, in particular a fast parameter (as TG are, compared, for example, with LDL-C) during a hyperacute condition (AMI). The Authors correctly state in their 'limitations' section that serum TG levels are not likely the final trigger of AMI, since subjects with higher TG levels on admission did not exhibit the morning pattern of AMI in the weekend. It is possible that this interesting observation, however, may have different and deepest implications. Many recent studies have investigated, at the molecular level, the structure of the peripheral circadian oscillator intrinsic to the myocardiocyte, along with the possible desynchronization action operated by serum TG (xxxx). Such aspects should be appropriately discussed. **One-year mortality according to AMI onset time** The finding that patients with an afternoon onset of AMI had the worst one-year mortality is interesting. On the other hand, it has been observed that morning infarctions are characterized by higher fatal outcome, independent of site and size of infarction (Manfredini et al, Am J Emerg Med 2004). It could be interesting to discuss wheher the OACIS registry has data on immediate mortality of patients with morning vs. afternoon-evening onset of AMI. **Conclusions** At now, and also after this study, it is somewhat difficult to make definite sense of results in this topic of study, notably the possible effect of TG. I appreciate a the appropriate caution expressed by the Authors in their conclusive remarks.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Muller Olivier
Institution and Country University of Lausanne
Please state any competing interests or state 'None declared': Competing interest (similar publications)

In this retrospective study based on 7755 consecutive patients with a known time of symptom onset, Ryuya Edahiro et al investigate the factors influencing circadian patterns of acute myocardial infarction onset. They observe that AMI onset exhibited bimodality and authors think that this distribution could be influenced by several lifestyle-related factors. In particular, they conclude that the subpopulation with admission TG levels ≥ 150 mg/dl was considered to have a high frequency of AMI onset in the morning.

We greatly appreciate your sincere review. We have tried to improve our manuscript according to your important comments and suggestions.

1) A circadian distribution of TG levels is known and described. Therefore, different levels of TG levels in blood samples taken at admission could be expected, as in a population without AMI.

We have added description about this in the text (Page 11, Lines 11-14; Page 20, Lines 1-3; Page 20, Lines 16-17, and eFigure2).

2) Authors should provide a figure with the circadian distribution of TG level based on hour oh symptom onset.

Cosinor-analysis revealed that the amplitude of serum TG levels on admission in patients with AMI didn't have circadian variation (p=0.52). We have added this result in the text as eFigure 2.

3) How many patients are there with TG > 150 mg/dl ? It seems that they are only a minority (Table 1 : Triglycerides (mg/dl) : 92 (58-142)

The number of patients with TG≧150mg/dl was 1473, and that of TG<150mg/dl was 5055. Although these numbers were already shown in Figure3 and eTable2 of the original manuscript, we have added description in the text of the revised manuscript (Page 13, Line 11; Page 14, Line 6).

4) Authors simply show that among patients with TG levels ≥ 150 mg/dl, the morning peak is more apparent than among the overall population. Nevertheless, with the provided data, they can not conclude that (Page 12) “serum TG levels on admission (…) had a statistically significant influence on the circadian pattern of AMI onset. In fact, even patients with TG levels < 150 mg/dl have the same morning peak (see eTable 1).

From the statistical point of view, the hierarchical likelihood ratio test revealed that TG levels on admission had statistically significant influence on circadian pattern of AMI onset (p<0.001). However, as the Reviewer pointed, the word ‘influence’ might be misleading. Thus, we have changed this sentence from “serum TG levels on admission (…) had a statistically significant influence on the circadian pattern ….” to “serum TG levels on admission (…) had a statistically significant association with the circadian pattern ….” (Page 13, Lines 2-5).

5) In eTable 1, the sub-group TG ≥150 mg/dl have a second Peak earlier than the first Peak ?? Of importance, the 95% CI is 2 :18 - 14:18, which is much more importante compared to all the other 95% CI. Could the authors explain these values ?

As the Reviewer suggested, this presentation was misleading. As we stated in the original manuscript

(Page 13, Lines 9-16), we interpreted that the sub-group TG ≥150 mg/dl had only one peak in the morning, although the likelihood ratio test identified two peaks in the morning in this subgroup. Therefore, we have described both peaks in this subgroup as the primary peak in eTable1 in the revised manuscript. Thank you very much for this important comment.

6) In the present study, patients with an afternoon onset of AMI had the worst one-year mortality. They compare their results with Bae et al (Korean Circ J.2010;40:616-24), which reported that patients with evening onset AMI had the worst one-year mortality in association with poor baseline clinical caracteristics. Nevertheless, they should compare their results with other recent studies based on circadian rhythms and STEMI patients, like Holmes et al (Circ Cardiovasc Qual Outcomes. 2010;3:382-389)

It the present study, the results were similar in the subgroup of STEMI patients (Page 15, Lines 15-16). According to the Reviewer's comment, we have cited papers by Holmes et al (Circ Cardiovasc Qual Outcomes. 2010;3:382-389) and Manfredini et al (Am J Emerg Med 2004;22:555-9) and compared our results with their results (Page 23, Lines 1- Page 24, Lines 3).

7) Regarding mortality, an interpretation with the provided data is difficult in the absence of data regarding delays (JAMA. 2000;283:2941–2947 ; Time is myocardium and time is outcomes).

As the Reviewer suggested, data regarding delays is very important because longer door-to-balloon time in STEMI patients was associated with poor mortality (JAMA.2000;283:2941–2947), and shorter onset-to-treatment time in AMI patients was associated with better prognosis (BMJ. 2012;344:e3257, Am J Cardiol. 1998;82:259-64). Unfortunately, we don't have information of door-to-balloon time or symptom-onset-to-balloon time, but have data of onset-to–admission time; the onset-to-admission time was longest in the nighttime onset [0:00-5:59 h] group, a consistent finding with the previous study (Circ Cardiovasc Qual Outcomes. 2010;3:382-389). Therefore, we have employed onset-to–admission time to make further analysis (Figure4, eTable3). As a result, mortality was not necessarily worse in the afternoon onset [12:00-17:59 h] group even after stratification with onset-to-admission time, suggesting that onset-to-admission time did not greatly affected the association between onset hours and mortality in the present study. Therefore, we have decided not to describe in detail about this in the revised manuscript. Thank you very much again for this important comment.

Reviewer Name Roberto Manfredini
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Department of Medical Sciences
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Please state any competing interests or state 'None declared': None declared

The Authors aimed to investigate the possible influence the circadian pattern of acute myocardial infarction (AMI) of a series of lifestyle-related factors.
The study has been performed in Japan, and is based on the data of the Osaka Acute Coronary Insufficiency Study (OACIS), and includes 7755 patients.
Main significant results are the finding of a bimodality of circadian pattern of AMI onset, and a strong relationship of triglyceride (TG) levels with such pattern.
I have sincerely appreciated the study, dealing with an interesting topic, and the manuscript is interesting and well written.
Some considerations and suggestions will follow.

Thank you very much for your wonderful comments and concerns. We have tried to improve our manuscript according to your suggestions.

Bimodal pattern of AMI onset: morning and nighttime peaks
This aspect represents further confirmation of many studies worldwide (some of them appropriately cited in the reference section). The morning peak , as well the less pronounced evening one, have been widely reported in the literature, and also demonstrated in cerebrovascular accidents, i.e., ischemic and hemorrhagic stroke (Manfredini et al, Chronobiol Int 2005). Again, also the presence of a Monday peak is well known.
Interestingly, the same morning and Monday pattern has been reported also for other non-AMI acute coronary syndromes, e.g., Tako-tsubo cardiomyopathy (Citro et al, J Am Coll Cardiol 2009; Manfredini et al, Am J Emerg Med 2010).

Impacts of lifestyle-related factors on circadian patterns of AMI onset
The impact of several major risk factors (age, sex, hypertension, diabetes, lipids) on the circadian pattern of stroke has been investigated several years ago both regarding the circadian variation (Casetta et al, Arch Neurol 2002), and the Monday peak (Manfredini et al, Am J Emerg Med 2008).
As for the possible impact of serum TG on the circadian pattern of AMI, perhaps the general consideration of TG as a risk factor of cardiovascular disease, even if the easiest, is not fully convincing to explain a circadian interference. Again, the evaluation of a blood lipid marker in 'acute' conditions is doubtful, in particular a fast parameter (as TG are, compared, for example, with LDL-C) during a hyperacute condition (AMI).
The Authors correctly state in their 'limitations' section that serum TG levels are not likely the final trigger of AMI, since subjects with higher TG levels on admission did not exhibit the morning pattern of AMI in the weekend.

It is possible that this interesting observation, however, may have different and deepest implications. Many recent studies have investigated, at the molecular level, the structure of the peripheral circadian oscillator intrinsic to the myocardiocyte, along with the possible desynchronization action operated by serum TG (xxxx). Such aspects should be appropriately discussed.

Thank you very much for your thoughtful comments. We have added description about the possibility regarding the peripheral clock modulation by TG in the Discussion section of the revised manuscript (Page 21, Lines 17- Page 22, Lines 6).

One-year mortality according to AMI onset time
The finding that patients with an afternoon onset of AMI had the worst one-year mortality is interesting. On the other hand, it has been observed that morning infarctions are characterized by higher fatal outcome, independent of site and size of infarction (Manfredini et al, Am J Emerg Med 2004). It could be interesting to discuss wheher the OACIS registry has data on immediate mortality of patients with morning vs. afternoon-evening onset of AMI.

We greatly appreciate this comment. We have revised our discussion with citing papers suggested by the Reviewers (Page 23, Lines 1- Page 24, Lines 3, ref. 42 and ref. 44), although the reasons why the observations were different among the studies were unclear. As for the immediate (30-day) mortality, Kaplan-Meier survival analysis demonstrated that the morning-onset (6:00-11:59 h) and afternoon-onset (12:00-17:59 h) group tended to have worse 30days mortality than the other groups in the present study. However, this was not statistically significant (log rank test, p=0.065). Therefore, we didn't include this result in the manuscript. We greatly appreciate your understanding.

Conclusions
At now, and also after this study, it is somewhat difficult to make definite sense of results in this topic of study, notably the possible effect of TG. I appreciate a the appropriate caution expressed by the Authors in their conclusive remarks.

Thank you very much for your thoughtful comment. We have expressed the caution about the possible effect of TG in the conclusion section as “However, cautions are warranted to interpret our results and confirmation in other cohorts is required.” (Page 25, Lines 16- Page 26, Lines 1).

VERSION 2 – REVIEW

REVIEWER	Roberto Manfredini University of Ferrara School of Medicine Department of Endocrinology and Internal Medicine Italy
REVIEW RETURNED	02-May-2014

- The reviewer completed the checklist but made no further comments.