Response to the letter to the editor regarding the study "Impact of time of onset of symptom of ST-segment elevation myocardial infarction on 1-year rehospitalization for heart failure and mortality" published in the *American Heart Journal*

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We welcome the comments made by Rosseberg et al[1] regarding our article which showed that patients with STEMI onset outside-office-hours had an increased risk of death and heart failure (HF) rehospitalisation at 1 year. We acknowledge the possibility that factors other than time of presentation may have influenced these findings, including delays in symptom-to-door time and door-to-balloon (DTB) time outside-of-office hours, and differences in the quality of care between admitting hospitals, and have undertaken additional analyses to investigate this.

As expected, we found that both symptom-to-door and DTB times, were increased at overnight 00:00AM-5:59AM (see Table 1), and both factors were predictors of 1-year mortality and HF rehospitalization in STEMI patients. However, the admitting hospital was not a predictor of clinical outcomes, suggesting that the quality of care (in terms of PPCI expertise and volume and outside-office-hours workflows), had no impact on post-STEMI outcomes. Crucially, we noted that even after adjusting for symptom-to-door and DTB times, and the admitting hospital, there was still a circadian variation in both 1 year rates of mortality and HF rehospitalization, with ~30% higher rates of death (between 06:00PM-11:59PM) and ~40 to 50% higher rates of HF rehospitalization (between 06:00PM-11:59PM, 12:00PM-05:59PM, and 00:00AM-5:59AM), when compared to the time period 06:00AM-11:59AM (see Table 2). This new analyses suggest that the observed increased risk in both 1-year mortality and HF rehospitalization are present despite the prolongation in symptom-to-door and DTB times observed outside-of-office hours and irrespective of potential quality of care differences among admitting hospitals.

We appreciate that the accuracy in recording symptom onset is of paramount importance when investigating for correlations between ischemic times and clinical outcomes following STEMI. In our national registry, self-reported times of symptom onset were ascertained by the attending physician in the emergency department,

and we excluded 722 out of 12,453 patients from the analysis as their symptoms had been defined as being atypical, mild, transient or intermittent. However, we are unable to address the concern over whether the recorded symptom onset time referred to the beginning of symptoms or the time of waking up, as this information was not collected in our registry.

In summary, in our national registry based analysis, we found that the time of symptom onset influenced 1-year clinical outcomes including death and HF rehospitalization, with 30 to 50% higher rates of both outcomes outside-office-hours, that persisted even after adjusting for potential quality of care differences among the admission hospitals (such as PPCI volume, symptom-to-door and DTB times). We thank Rosseberg et al[1] for their interest and for providing us with the opportunity to share further insights into our analysis.

Reference

1. Letter by Nora Rossberg, Ali Kirresh, Mahmood Ahmad

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Table 1.

	Symptom onset time				p-value
	06:00AM-11:59AM (n=3787)	12:00PM-05:59PM (n=2909)	06:00PM-11:59PM (n=2656)	00:00AM-05:59AM (n=2379)	
Door-to-balloon time in minutes, median (IQR)	63 (47-86)	64 (48-88)	69 (54-92)	70 (54-93)	<0.001
Symptom-to-door time in minutes, median (IQR)	127 (71-234)	109 (59-208)	112 (61-244)	135 (63-338)	<0.001
Symptom-to-balloon time in minutes, median (IQR)	190 (125-301)	172 (112-281)	183 (122-314)	206 (131-405)	<0.001

Table 2.

	1-year mortality		1-year rehospitalization for heart failure	
Unadjusted	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
06:00AM-11:59AM	1.00		1.00	
12:00PM-05:59PM	1.11 (0.93-1.32)	0.245	1.28 (0.97-1.70)	0.083
06:00PM-11:59PM	1.40 (1.18-1.66)	<0.001	1.50 (1.14-1.99)	0.004
00:00AM-05:59AM	1.16 (0.97-1.40)	0.106	1.83 (1.39-2.41)	<0.001
Adjusted*	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
06:00AM-11:59AM	1.00		1.00	
12:00PM-05:59PM	0.94 (0.76-1.16)	0.583	1.41 (1.04-1.92)	0.028
06:00PM-11:59PM	1.29 (1.06-1.57)	0.012	1.43 (1.05-1.95)	0.023
00:00AM-05:59AM	1.06 (0.86-1.31)	0.583	1.51 (1.12-2.04)	0.007

*Adjusted for age, gender, ethnicity, history of diabetes, history of hypertension, smoking status, history of MI or revascularization, anterior STEMI, cardiopulmonary resuscitation, Killip class, elevated first troponin, admitting hospital, symptom-to-door time, and door-to-balloon time.