SUPPLEMENTAL MATERIAL

Independent association between symptom onset time and infarct size in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Circadian variation in infarct size by center

Circadian variation in infarct size by center is shown in Supplemental Figure 1. In both centers, infarct size was largest for patients with symptom onset during the night and lowest for patients with symptom onset during the morning and early afternoon. However, the curve of Center B seems to be somewhat displaced to the right as compared with Center A. Furthermore, a second smaller evening peak in infarct size was seen in Center B but not in Center A. The between-center difference in the circadian pattern of infarct size was not statistically significant (p -interaction=0.379).

Supplemental Figure 1. Circadian variation in infarct size by center

Sensitivity analysis 1

As a sensitivity analysis, the analysis reported in Table 3 of the manuscript was repeated with the omission of body mass index (Supplemental Table 1). The rationale for performing this sensitivity analysis was that body mass index was the only baseline variable that was missing in more than 10% of patients. As is apparent from the table, the results were similar to those reported in the manuscript.

Supplemental Table 1. Independent predictors of infarct size with omission of body mass index

	Estimate (95% CI)	p Value	p-interaction*
<i>Model A: adjusted for baseline characteristics†</i>			
Symptom onset time	–	0.003	
Prior myocardial infarction	–19% (–28; –7.7)	0.001	0.034
Prior PCI	–20% (–29; –8.4)	0.001	0.279
<i>Model B: adjusted for ischemic time</i>			
Symptom onset time	–	0.015	
Ischemic time (per doubling)	+13% (+8.4; +18)	<0.001	
<i>Model C: adjusted for baseline characteristics† and ischemic time</i>			
Symptom onset time	–	0.013	
Prior myocardial infarction	–19% (–29; –8.2)	0.001	0.038
Prior PCI	–18% (–28; –6.5)	0.003	0.540
Ischemic time (per doubling)	+11% (+6.9; +16)	<0.001	
<i>Model D: adjusted for baseline characteristics†, ischemic time, and hemodynamic status on admission</i>			
Symptom onset time	–	0.007	
Prior myocardial infarction	–18% (–28; –6.2)	0.004	0.011
Prior PCI	–17% (–28; –4.8)	0.008	0.525
Ischemic time (per doubling)	+9.7% (+5.1; +14)	<0.001	
Systolic blood pressure <90 mmHg	+31% (+12; +53)	0.001	
Heart rate >100 bpm	+19% (+6.6; +33)	0.002	

CI = confidence interval; PCI = percutaneous coronary intervention

*P value for interaction with symptom onset time; †All variables listed in Table 1 of the manuscript, accounting for the interactions with prior myocardial infarction and prior percutaneous coronary intervention

Sensitivity analysis 2

In a second sensitivity analysis, we applied similar eligibility criteria as reported in a prior study (Reiter et al., 2012). We now also excluded patients with ischemic time >6 hours (n=1116), preprocedural Thrombolysis In Myocardial Infarction (TIMI) flow >0 (n=2655), prior myocardial infarction (n=331), prior coronary artery bypass grafting (n=30), and postprocedural TIMI flow <1 (n=43). In the remaining population (n=2624), we repeated the analyses reported in the manuscript.

As can be expected, infarct size was larger in this subpopulation. Nonetheless, we found significant circadian variation in infarct size ($p=0.004$) with a peak for symptom onset at 05:00 in the morning (peak creatine kinase [CK] 1950; 95%CI 1766-2153) and nadir at 13:00 (peak CK 1554; 95%CI 1438-1679; relative reduction 20%; Supplemental Figure 2), thus representing a slight shift to the right as compared with the original analysis reported in the manuscript. Circadian variation was also found in ischemic time ($p<0.001$; Supplemental Figure 2).

Supplemental Figure 2. Circadian variation in infarct size and ischemic time

The association between symptom onset time and infarct size persisted in multivariable analysis (Supplemental Table 2). No more subgroup interactions were found in this subpopulation that only consisted of patients with a first myocardial infarction. No association was found between symptom onset time and 30-day mortality (p=0.516) or 1-year mortality (p=0.521).

Supplemental Table 2. Independent predictors of infarct size after additional exclusions

	Estimate (95% CI)	p Value
<i>Model A: adjusted for baseline characteristics*</i>		
Symptom onset time	–	0.008
<i>Model B: adjusted for ischemic time</i>		
Symptom onset time	–	0.018
Ischemic time (per doubling)	+22% (+13; +31)	<0.001
<i>Model C: adjusted for baseline characteristics* and ischemic time</i>		
Symptom onset time	–	0.029
Ischemic time (per doubling)	+26% (+16; +37)	<0.001
<i>Model D: adjusted for baseline characteristics*, ischemic time, and hemodynamic status on admission</i>		
Symptom onset time	–	0.028
Ischemic time (per doubling)	+25% (+15; +36)	<0.001
Systolic blood pressure <90 mmHg	+38% (+12; +70)	0.003
Heart rate >100 bpm	+34% (+12; +60)	0.001
CI = confidence interval; PCI = percutaneous coronary intervention		
*All variables listed in Table 1 of the manuscript		

Supplemental Reference

Reiter R, Swingen C, Moore L, et al. (2012). Circadian dependence of infarct size and left ventricular function after ST elevation myocardial infarction. *Circ Res.* 110:105-10.