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Depression as Another Possible Explanation for Worse Outcomes in Myocardial Infarction During Off-Hours

We read with great interest the findings of Henriques et al. (1) regarding worse clinical outcomes for acute myocardial infarction (MI) patients treated with primary angioplasty during off-hours. In their otherwise excellent study, the investigators failed to measure depression or to mention it as another possible reason for the increased rates of failed angioplasty and 30-day mortality observed in those patients presenting between the hours of 1800 and 0800. Depression is common among patients with coronary disease (2), and depressed patients are more likely to develop initial MI symptoms off-hours (3). Depressed patients admitted for MI are at significantly increased risk for mortality (2) and for repeat coronary revascularization (4). Moreover, depression is associated with perturbations of circadian rhythms in patients with and without coronary disease (5). Thus, in addition to the reasons offered by the investigators (1), depression may be another explanation for the worse outcomes observed in patients presenting off-hours.

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Circadian Variations in Outcome of Primary Percutaneous Coronary Intervention

We read with interest the report by Henriques et al. (1) regarding circadian variations in outcomes of primary angioplasty for acute

myocardial infarction. The investigators cite a higher angioplasty failure and a higher mortality in patients treated during the "off-hours" despite similar baseline characteristics and procedural delays compared with patients treated during daytime. The researchers also point out that only 23% of the total cohort was treated during the night. This suggests a potential selection bias of the patients treated at night, particularly among the 11 community hospitals referring patients to the single percutaneous transluminal coronary angioplasty (PTCA) center involved. In a previous smaller study (2), addressing a cohort of consecutive ST-elevation myocardial infarction patients admitted to a single center performing primary percutaneous coronary intervention (PCI), we found that 61% of the patients were treated during off-hours (also counting weekend hours), a percentage perfectly in line with the proportion of off-hours during the week (64%). In that study, despite worse baseline characteristics of patients admitted during off-hours, patients experienced almost identical procedural success rates (98% vs. 96% TIMI [Thrombolysis In Myocardial Infarction] 3 flow rates for "off" vs. business hours), predischARGE radionuclide left ventricular ejection fraction (51 ± 14 vs. $53 \pm 12\%$) and in-hospital death rates (7% vs. 5%) compared with patients treated during business hours ($p = \text{NS}$ for all comparisons).

As pointed out in the accompanying editorial in the *Journal* (3), the variations in patterns of care and outcomes reported by Henriques et al. (1) may be related to biological circadian variations but also to variations in health care delivery, particularly prehospital referral patterns and delays. We submit that the latter are more likely than the former. To explore this issue further and to minimize biases related to prehospital referral, we suggest that data be analyzed from several centers with a "captive" patient population (i.e., only one hospital serving a given population) and using primary PCI as the sole reperfusion therapy for ST-elevation myocardial infarction.

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REPLY

We appreciate Dr. Haas's as well as Dr. Steg's and their colleagues' interest and comments on our report concerning the different

outcome of primary PCI patients treated during the day versus during the off-hours (evening and night) (1). Dr. Haas's comment is very interesting, as it would possibly explain the apparent difference in mortality from a more biological perspective. Depression affects the circadian variation of onset of acute myocardial infarction (MI) and predicts revascularization over a longer period of time (2-4), implying that biological factors may be involved. Unfortunately, we did not measure prospectively the mental state prior to onset of acute MI.

The question remains whether this difference in outcome is due to biological factors or to factors related to seeking and/or administering care (5). Before returning to this question, it is important to emphasize that the variation of onset of acute MI has been demonstrated previously. In the very large ISIS-2 trial, with >17,000 patients (6), there was a rise of onset of acute MI from 0600 h, which lasted until 1800 h, after which there was a fall in onset of acute MI until 0600 h. Our data are compatible with these findings. Therefore, the majority of patients with acute MI will be treated during the day (0800 to 1800 h). Circadian variation and different outcomes in patients with thrombolysis have been published and discussed in our study (1) and in the accompanying editorial (5). With respect to different coagulation states during the day, it is important to point out that we did not find a difference in TIMI-2 and -3 flow before angioplasty, suggesting that coagulation may not be an important factor. Heart failure also seems to occur more frequently during the night compared with during the day, suggesting a biological factor (7). However, the question "Is it biology or care?" has not yet been answered definitively. We, however, did not find a difference in the care delivered.

Dr. Steg and colleagues argue that there was no difference in outcome in their study (8), when off-hours were compared with routine day hours. Their cohort comprised only 288 patients, perhaps making the study underpowered to detect a difference. Furthermore, in Dr. Steg's study, off-hours also comprised day hours during the weekend. We only analyzed our data with respect to day and night as this seems a more biological division. Both the number of patients studied and the division used to analyze off-hours and routine hours may have influenced the outcome of Dr. Steg's study. We further analyzed whether this mortality difference was present in referred patients and nonreferred patients. In both referred and nonreferred patients, mortality was higher when treated between 1800 and 0800 h, compared with

between 0800 and 1800 h. Mortality in referred patients was 2% versus 6% ($p = 0.01$) and in nonreferred patients 2% versus 3% ($p = 0.37$), respectively. The Breslow-Day test for heterogeneity was negative. Nevertheless, referral patterns may have affected our conclusions.

This underscores the need to restudy this issue in an even larger population.

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