

# Circadian Patterns of ST Elevation Myocardial Infarction in the New Millennium

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**Objective:** Nearly four decades ago, a circadian pattern of acute myocardial infarction (AMI) with a peak in the early morning waking hours was described. The goal of the present study was to determine whether major changes in lifestyle and significant advances in medical therapy have altered this pattern in the intervening years.

**Design:** Retrospective chart review.

**Setting:** Tertiary care hospital in central Wisconsin.

**Methods:** We examined circadian patterns of ST elevation myocardial infarction (STEMI) in 519 patients diagnosed with STEMI over a 5-year period. Time of symptom onset was obtained from patient self-reports in the medical record and was recorded over 24 hours.

**Results:** We observed a circadian pattern of STEMI occurrence with a morning peak at approximately 11:30 AM. This pattern was highly significant in patients who were not using beta-blockers ( $P < 0.0001$ ) and had no history of diabetes ( $P < 0.0001$ ), but was otherwise absent. The circadian pattern appeared to be attenuated in patients of a younger age, female gender, or who used statins or aspirin. Peak STEMI occurrence was earlier in smokers than non-smokers.

**Conclusions:** Despite significant lifestyle changes and medical advances in the nearly four decades since a circadian pattern of AMI occurrence was first described, patients with STEMI had a circadian pattern of symptom onset with a morning peak. Use of beta-blockers and a history of diabetes mellitus abolished this pattern. Other modifying factors, including medications, age, and gender attenuated, but did not abolish, the circadian pattern.

**Keywords:** Beta-blockers; Circadian rhythm; Diabetes; Myocardial infarction

Acute myocardial infarction (AMI) causes significant morbidity and mortality in the United States.<sup>1</sup> Several physiological factors can trigger AMI, and a number of these factors are known to fluctuate with circadian rhythm.<sup>2</sup> Circadian patterns of AMI were first described in 1976 by the World Health Organization Regional Office for Europe who reported a peak incidence in the onset of pain between 8:00 AM and 10:00 AM.<sup>3</sup> Similar results were reported by the Multicenter Investigation of Limitation of Infarct Size

(MILIS) study group in 1985,<sup>4</sup> which showed a circadian pattern of AMI with peak incidence in the morning between 6:00 AM and noon. Since 1985, several other groups have demonstrated a relationship between AMI and circadian rhythm with varying patterns.<sup>5-17</sup> Additionally, several factors have been found to modify or attenuate the circadian pattern of AMI including demographic factors,<sup>8,12</sup> medications,<sup>4,7,8,12,18,19</sup> comorbidities,<sup>8,12,20,21</sup> and lifestyle choices.<sup>8,12,17</sup>

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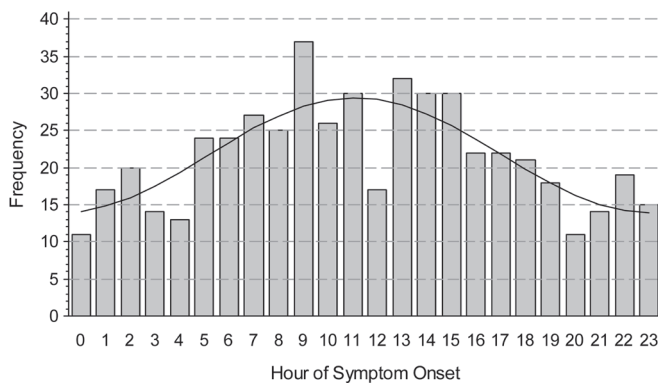
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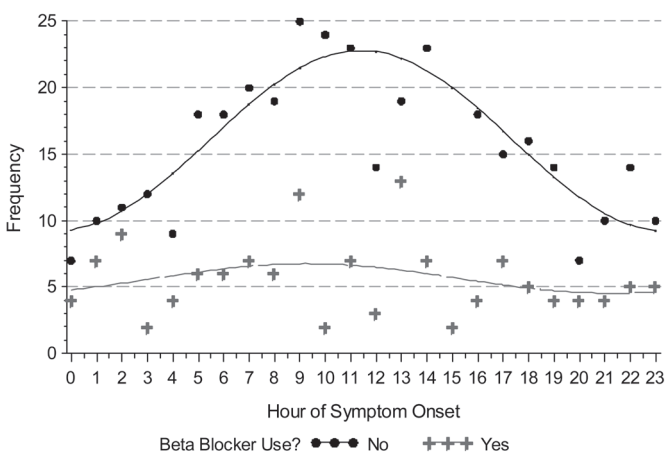


**Figure 1.** Observed and modeled counts by hour of STEMI symptom onset. Hour of onset was modeled using a single-period sine-cosine function.

In the nearly four decades since the first report of circadian patterns of AMI, lifestyles have changed significantly, and major advances in medical therapy have been made. Perhaps most notably, the rise in obesity and concurrent shift to a more sedentary lifestyle has resulted in an increase in several risk factors for cardiovascular disease and more patient prescriptions for related medications.<sup>22,23</sup> The goal of the present study was to determine whether circadian patterns of AMI persist despite these changes and to examine potential modifying factors.

### Materials and Methods

We conducted a retrospective, observational study involving 519 patients with STEMI at Ministry St. Joseph’s Hospital in Marshfield, Wisconsin. Patient data were abstracted from the cardiovascular data registry and adjudicated by review of individual patient records in the electronic medical record (EMR). The protocol was approved by the Marshfield Clinic Institutional Review Board.



**Figure 2.** Time of STEMI symptom onset in patients who did and did not use  $\beta$ -blockers.  $\beta$ -blocker use abolishes the circadian pattern. Observed (points) and modeled (line) counts are shown by hour of STEMI symptom onset. Hour of onset was modeled using a single-period sine-cosine function.

### Study Population

The patient population included male and female patients ages 18 years and older who presented with chest pain between January 1, 2006 and December 31, 2010 and were subsequently diagnosed with STEMI. STEMI diagnosis was based on electrocardiogram (EKG) criteria including ST-segment elevation of  $\geq 1$  mm (0.1 mV) in 2 or more adjacent limb leads or  $> 2$  mm in the precordial leads and positive cardiac biomarkers (troponin/CK-MB). Patients with insufficient or unclear data regarding symptom onset or  $< 1$  year of follow-up were excluded.

### Data Collection

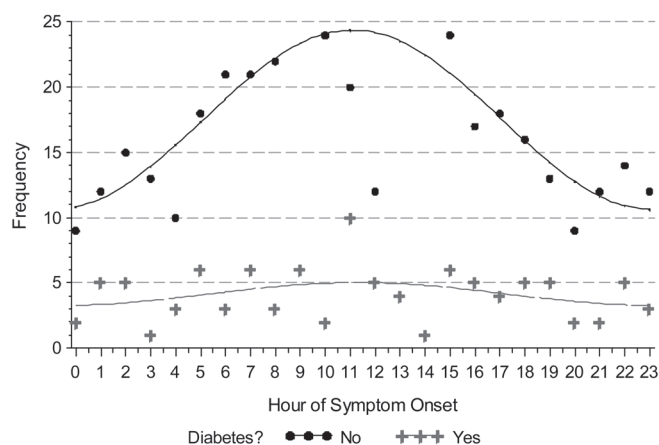
Time of onset of chest pain and symptoms of myocardial infarction were obtained from patient self-reports recorded by emergency medical service (EMS) or emergency department staff. For 11 patients who presented with non-specific symptoms, time of symptom onset was not recorded and time of call to EMS or EKG time was noted instead. Additional data collected included information about onset of chest pain, age, gender, past medical history (diabetes mellitus, congestive heart failure [CHF], dyslipidemia, hypertension), medications (aspirin, clopidogrel, beta-blockers, statins), and outcomes (death, CHF, stroke) during hospital stay and in the following year.

### Statistical Analyses

Standard descriptive statistics were used to summarize important characteristics of the STEMI cohort by time period of symptom onset. Preliminary comparisons were based on Chi-square tests for frequencies and the rank sum test for continuous variables. In the primary study analyses, event frequencies were analyzed by time of onset in keeping with a circular distribution over the 24-hour clock. The Rayleigh test was used to evaluate the hypothesis of a uniform distribution of times, and the hour of onset was modeled using a single-period sine-cosine function (a higher period sinusoid was evaluated, but did not fit the data as well based on the adjusted  $R^2$  criterion). All analyses were conducted using SAS version 9.2 statistical software. References to statistical significance are based on the 5% level of significance ( $P < 0.05$ ) in two-sided tests.

### Results

We observed a circadian pattern of STEMI incidence with onset in the late morning hours. Single-period sine-cosine modeling over the entire 24-hour period demonstrated a morning peak occurring at approximately 11:30 AM (figure 1). However, use of beta-blockers and a history of diabetes mellitus abolished this pattern. While the circadian pattern of STEMI occurrence was highly significant in patients who did not use beta-blockers ( $P < 0.0001$ ), it was absent in those who did ( $P = 0.4024$ ) (figure 2). Similarly, patients with no history of diabetes mellitus displayed a clear circadian pattern ( $P < 0.0001$ ), which was absent in diabetic patients ( $P = 0.3495$ ) (figure 3). The circadian pattern of STEMI was similar in smokers and non-smokers, except that smokers had an



**Figure 3.** Observed (points) and modeled (line) time of STEMI symptom onset in patients with and without a history of diabetes mellitus. Hour of onset was modeled using a single-period sine-cosine function. The circadian pattern is absent in diabetic patients.

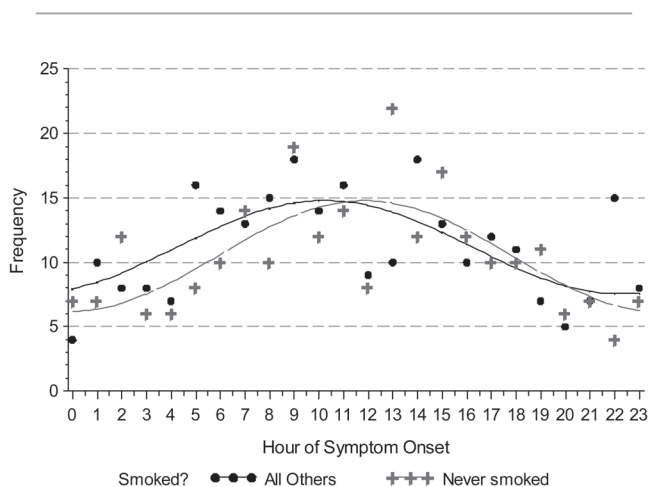
earlier peak than that of non-smokers (figure 4). Several factors were found to attenuate the circadian pattern in STEMI incidence. The circadian pattern was present, but attenuated, in patients of a younger age, female gender, or who used statins or aspirin (figure 5). No significant relationships were observed between outcomes, including death, CHF, or stroke, and time of onset of chest pain during initial hospital stay or over 1 year of follow-up. Other patient comorbidities and clinical outcomes are depicted in Table 1 and no correlation between time of symptom onset and any events were noted.

### Discussion

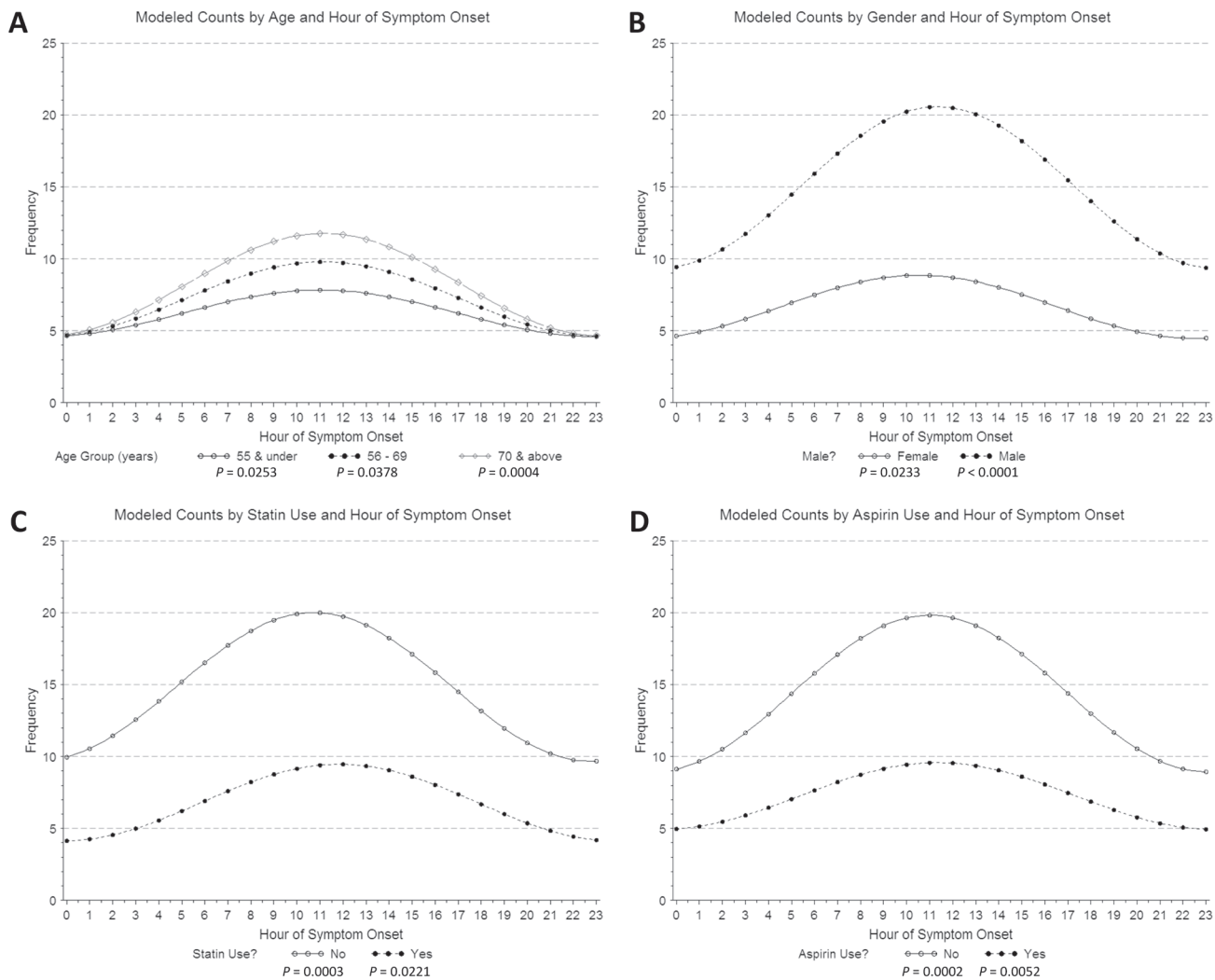
Since the 1970s, many studies have demonstrated a circadian pattern in AMI onset with a peak occurrence in the morning.<sup>3-15,17,24</sup> The past four decades have seen major changes in lifestyle and significant improvements in medical intervention. It is generally accepted that poor diet and a shift toward a more sedentary lifestyle have resulted in a dramatic rise in obesity in the United States and a concurrent rise in obesity-related comorbidities.<sup>22,23</sup> Comparison of population demographics in studies of circadian rhythm and MI over time are telling of these changes. In 1989, Hjalmarsen et al observed a 16% rate of obesity in study patients,<sup>6</sup> and in 1992 Tofler et al noted an obesity rate of 13.9%.<sup>9</sup> By 1997, Sayer et al observed an obesity rate of 21%,<sup>12</sup> consistent with the 19.1% observed in the present study. Similarly, while Tofler et al observed hypertension in 38.3% of patients in 1992,<sup>9</sup> rates had risen to 56.1% of patients in a 2010 study by Holmes et al,<sup>17</sup> and 61.1% in the present study. In addition to the increase in obesity-related comorbidities, an increased utilization of cardioprotective pharmaceuticals has also been observed over time. In 1993, the American Heart Association (AHA) officially recommended use of aspirin as a therapeutic agent for the prevention of cardiovascular disease.<sup>25</sup> We noted an increase in aspirin use from 10.8% in the 1992 study by Tofler

et al<sup>9</sup> to 13% in the 1997 study by Sayer et al,<sup>12</sup> and 33.5% in the present study. The increase in beta-blocker usage over time appears to be even greater, with a 4.5% rate of use in the 1985 study by Muller et al,<sup>2</sup> rising to approximately 17% to 18% in studies by Hjalmarsen et al<sup>6</sup> in 1989 and Tofler et al<sup>9</sup> in 1992, and 26.2% in the present study. In addition to changes in lifestyle and medical intervention, significant progress has also been made in the past several years in recognizing differences in symptoms of ischemic heart disease in women.<sup>26</sup> Accordingly, the number of female subjects noted in studies over time has increased from 18.4% in a 1989 study by Willich et al<sup>7</sup> to 21% in 1997 by Sayer et al,<sup>12</sup> and 31% in the present study. Our findings are consistent with those that have appeared in the literature over time,<sup>11,13,15,17</sup> and suggest that despite major changes in lifestyle and significant improvements in medical care over the past nearly four decades, the effects of circadian rhythm on AMI occurrence have remained constant.

Several factors that are considered triggers of cardiovascular disease undergo circadian variation.<sup>2</sup> In the morning, sympathetic activity<sup>10,27-29</sup> and platelet aggregability increase while plasma fibrinolytic activity decreases.<sup>30-37</sup> These changes result in altered hemostasis and an imbalance between myocardial oxygen supply and demand, potentially leading to AMI. Other changes noted in the morning, especially with assumption of the upright posture, include increased heart rate, sympathetic tone, renin activity, and plasma concentrations of cortisol, epinephrine, norepinephrine, and angiotensin II.<sup>9,30,32,38,39</sup> Sympathetic activity may further enhance platelet aggregation,<sup>40</sup> and cortisol may increase sensitivity of the coronary arteries to the vasoconstrictor effects of catecholamines.<sup>41,42</sup> Increased blood viscosity and platelet aggregability in the absence of a compensatory increase in circulating tissue-type plasminogen activator activity results in an environment of relative hypercoagulability. Additionally,



**Figure 4.** Observed (points) and modeled (line) time of STEMI symptom onset in patients who never smoked compared to all others. Hour of onset was modeled using a single-period sine-cosine function. The morning peak in STEMI occurrence is earlier in those with a history of smoking.



**Figure 5.** Time of STEMI symptom onset in patients by (A) age, (B) gender, and (C) statin and (D) aspirin use. Hour of onset was modeled using a single-period sine-cosine function. The circadian pattern is present, but attenuated in younger, female, statin using, and aspirin using patients.

recent studies have demonstrated that clock genes in human cardiac tissue display significant time-dependent transcriptional variation with peak expression of some clock genes and trough expression of others coinciding with myocardial incidents.<sup>43</sup> Morning hours may also represent nadir levels of some cardioprotective medications. Together, these hemostatic changes, changes in gene expression, and external triggers may create a shearing stress and cause rupture of vulnerable coronary atherosclerotic plaques in the morning, when an elevated prothrombotic state already exists.<sup>44-49</sup>

In addition to the morning peak, a secondary peak of AMI occurrence in the evening has been identified in several earlier studies.<sup>4-6,10,24</sup> This peak is notably absent in our study as well as in two contemporary studies published in 2007 and 2010 by Leiza et al<sup>15</sup> and Holmes et al,<sup>17</sup> respectively. In 1989, Muller et al<sup>2</sup> hypothesized that the presence of this secondary evening peak was indicative of population-wide

synchronization of additional triggers for AMI, similar to those identified for the morning peak, such as the evening meal. It is possible that changes in lifestyle over the past several years have contributed to a gradual loss in this peak due to a loss of population-wide synchronization of such triggers in the evening time, while synchronization upon waking still exists.

The factors that modify the circadian pattern of AMI occurrence identified in the present study are similar to those reported in the literature.<sup>4,7,8,12,15,17-21</sup> It is interesting that while use of beta-blockers and a history of diabetes completely abolished the presence of a circadian pattern of AMI onset, other modifying factors including age, gender, statin use, and aspirin use merely attenuated the pattern. Beta-blockers are known to prevent increases in sympathetic activity, catecholamine concentrations, heart rate, blood pressure, and cardiac oxygen demand. Similarly, there may be decreased autonomic function in diabetic patients. Depression of these

**Table 1.** Patient characteristics by period of symptom onset.

	n	Time Period		
		00:01 – 08:00	08:01 – 16:00	16:01 – 24:00
Number Subjects	519	158	224	137
Male	359	66.5%	70.5%	70.1%
Median Age in Years (Range)		64.6 (29 – 94)	63.0 (32 – 94)	63.7 (26 – 92)
Never Smoked	251	45.6%	50.4%	48.2%
Diabetic	99	19.0%	16.1%	24.1%
Hypertensive	317	62.0%	62.9%	56.9%
Heart Failure	22	4.4%	4.5%	3.6%
MI/Coronary Artery Disease	101	16.5%	17.9%	25.5%
Coronary Artery Bypass Graft Surgery	115	24.1%	21.4%	21.2%
Stroke	37	7.6%	7.6%	5.8%
Cardiogenic Shock	98	16.5%	17.0%	24.8%
Aspirin Users	174	34.2%	32.6%	34.3%
Beta-blocker Users	135	29.1%	22.8%	27.7%
ACE Inhibitor or ARB Users	114	13.9%	25.4%	25.5%
Statin Users	163	26.6%	32.6%	35.0%
Median Ejection Fraction (Range)		48.0 (10 – 75)	50.0 (17 – 72)	45.0 (15 – 75)
Mortality in Hospital	37	7.6%	6.3%	8.0%
Mortality Within 1 Year	62	12.7%	9.4%	15.3%

systems, and thus, suppression of common morning triggers of AMI may explain the absence of the circadian patterns in patients on beta-blockers and those with a history of diabetes mellitus. The absence of a circadian pattern in patients taking beta-blockers has been remarkably consistent overtime and between studies, with several other groups observing a complete loss of circadian pattern in patients taking beta-blockers.<sup>4,7,12,18</sup> However, some have observed an attenuation or change in pattern, as opposed to complete loss.<sup>8,19</sup> Results in diabetic patients are more variable. Similar to our findings, Fava et al<sup>20</sup> and Sayer et al<sup>12</sup> found the circadian pattern of AMI to be absent in patients with diabetes. However, others have observed an attenuated or altered pattern<sup>8,21</sup> or even no effect of diabetes.<sup>18</sup> These differences may be attributable to the inherent difficulties in studying diabetic patients, as the effects of diabetes on other health conditions are dependent on a number of factors including length of time the person has been afflicted, glycemic control, and medication use, among others. We were unable to capture detail regarding medication use, insulin-dependence, or diabetes duration in the present study. Future studies of diabetes and circadian patterns of AMI including such information may prove particularly interesting.

Other factors that attenuated, but did not abolish, the circadian pattern of STEMI occurrence in the present study include age, gender, statin use, and aspirin use. While attenuation of the circadian pattern in younger or female patients has not been reported previously, Gilpin et al<sup>8</sup> did note a unique pattern of

occurrence in older and female patients with equal peaks of occurrence in the morning and evening. Others have not observed any effect of age or gender.<sup>15,18</sup> Attenuation of the circadian pattern in patients using statins and aspirin may be the result of the anti-inflammatory and anti-platelet properties of these medications, which may dampen the early morning triggers of AMI.

The circadian patterns of AMI onset observed in smokers also tend to vary by study. We did not observe attenuation of the pattern in smokers, rather a shift in the peak such that it occurred slightly earlier in smokers than in non-smokers. Hansen et al<sup>18</sup> observed no effect of smoking, while Sayer et al<sup>12</sup> observed a complete loss of the circadian pattern in smokers. Similar to our findings, Gilpin et al<sup>8</sup> and Holmes et al<sup>17</sup> observed changes in the pattern, but not loss. As with diabetes, the effects of smoking can also be difficult to study, as length of time as a smoker and packs per day can vary widely and may have an impact on the results.

In addition to examining factors that could modify the circadian pattern of STEMI occurrence, we also examined disease outcomes, including death, CHF, or stroke during initial hospital stay and over 1 year of follow-up. We observed no effect of time of STEMI onset on any outcomes. This finding is consistent with others which have shown that despite longer pre-hospital delays and longer time to treatment after arriving at the hospital in patients developing symptoms in the morning hours, there was no association between the circadian pattern of AMI onset and in-hospital death.<sup>17</sup>

The present study is limited by the retrospective nature of the data collection and use of subjective reports of time of chest pain onset. However, Willich et al<sup>46</sup> demonstrated that self-reported pain onset correlated well with enzymatic confirmation. Additionally, our results are likely to be influenced by survival bias as patients who died at home or before reaching the hospital were not included. Subgroups of patients on beta-blockers, antiplatelet agents, and statins were small, which may have limited statistical power. However, findings are consistent with those in the literature.

### Conclusion

Despite major medical advances and changes in lifestyle since the first reports of circadian patterns in AMI occurrence, we found that such a pattern still exists and that STEMI occurs most frequently in the morning hours. The circadian pattern of STEMI is absent, however, in patients on beta-blockers and with a history of diabetes mellitus and attenuated by several other medications and conditions.

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