

# Circadian Variation of Acute Myocardial Infarction and the Effect of Low-Dose Aspirin in a Randomized Trial of Physicians

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**Increased platelet aggregation in the morning and upon assuming an upright posture may account at least in part for the observed circadian variation in onset of acute myocardial infarction. The Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of alternate-day aspirin intake (325 mg) among 22,071 US male physicians, afforded the opportunity to assess this circadian pattern and examine whether it is altered by aspirin therapy. During a 5-year period of follow-up, 342 cases of nonfatal myocardial infarction were confirmed, of which the time of onset was available in 211 (62%). The placebo group showed a bimodal circadian variation in onset of myocardial infarction with a primary peak between 4:00 AM and 10:00 AM ( $p < 0.001$ ). In the aspirin group, however, this circadian variation was minimal ( $p = 0.16$ ), due primarily to a marked reduction in the morning peak of infarction. Specifically, aspirin was associated with a 59.3% reduction in the incidence of infarction during the morning waking hours, compared with a 34.1% reduction for the remaining hours of the day. The greater reduction was observed during the 3-hour interval immediately after awakening, a period with a risk of infarction twice that of any other comparable time interval ( $p < 0.001$ ). Aspirin intake was associated with a mean reduction in the incidence of infarction of 44.8% over the entire 24-hour cycle. These data support the hypothesis that increased platelet aggregability in the morning and upon arising contributes to the occurrence of myocardial infarction and that aspirin reduces the risk of infarction by inhibiting platelet aggregation during these critical periods. (*Circulation* 1990;82:897-902)**

**R**ecent epidemiological studies have demonstrated a circadian morning peak in the onset of disorders associated with intravascular thrombosis, acute myocardial infarction in particular.<sup>1-6</sup> Clinical studies have demonstrated a morning increase in platelet aggregability that appears to be related to assuming an upright posture.<sup>7-9</sup> Such findings raise the possibility of a causal association between morning increases in platelet aggregability and the observed increased relative frequency of morning thrombotic events. If

so, therapy with antiplatelet agents such as aspirin may be a method of preventing thrombosis during this critical period of increased platelet aggregation.

The circadian variation of the incidence of acute myocardial infarction and the effects of aspirin on this pattern were evaluated in the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of alternate-day aspirin intake (Bufferin, Bristol-Myers Products, 325 mg) among 22,071 US male physicians. Data from this trial have previously shown a 44.0% reduction in risk of first myocardial infarction among subjects assigned to the aspirin group.<sup>10-11</sup> In this report, we describe the frequency of nonfatal myocardial infarction by time of day and examine differences in this distribution among those in the aspirin group and those in the placebo group.

## Methods

A detailed description of the subjects and methods of the Physicians' Health Study has previously been reported.<sup>10-11</sup> Briefly, 22,071 US male physicians, aged 40-84 years and without a previous history of myocardial infarction, were randomly assigned in

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**TABLE 1. Comparison of Aspirin and Placebo Treatment Groups According to Baseline Cardiovascular Risk Factors at Time of Randomization**

Variable*	Aspirin group (n=11,037)	Placebo group (n=11,034)
Mean age (yr)†	53.2±9.5	53.2±9.5
Mean cholesterol level (mg/dl)†	212.0±44.5	212.0±45.6
Mean body mass index (kg/m <sup>2</sup> )†	24.9±3.1	24.9±3.0
Reporting hypertension (%)‡	11.8	12.0
Reporting high cholesterol (%)§	5.4	5.3
Diabetes mellitus (%)	2.3	2.2
History of angina pectoris (%)	1.3	1.2
Parental history of MI (%)	13.0	13.1
Current smoking (%)	11.0	11.1

MI, myocardial infarction.

\*All risk factors were self-reported.

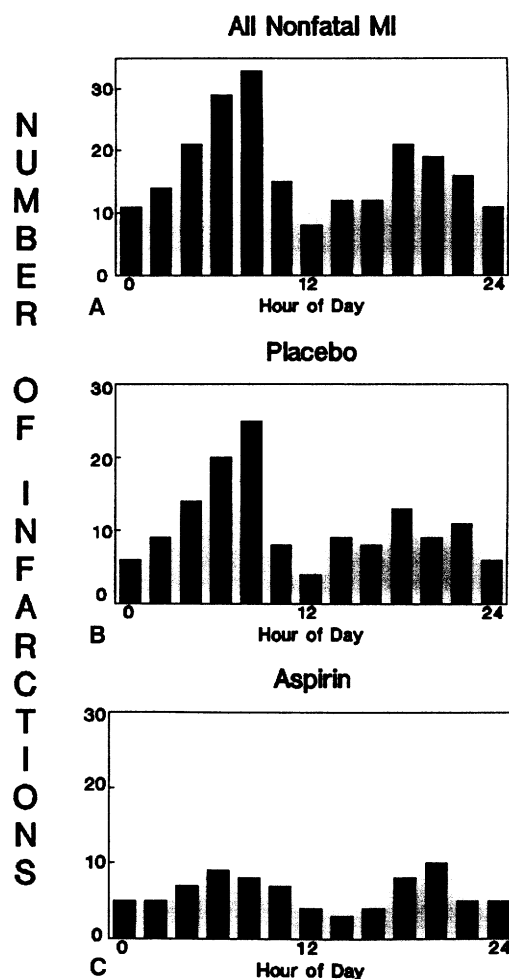
†Values are given as mean±SD.

‡Hypertension is defined as systolic  $\geq 160$  mm Hg or diastolic  $\geq 95$  mm Hg or currently treated.§High cholesterol is defined as  $\geq 260$  mg/dl or currently treated; this information available for approximately one third of subjects.

1982 to receive active aspirin ( $n=11,037$ ) or aspirin placebo ( $n=11,034$ ). During a follow-up period of 60.2 months, 342 cases of nonfatal acute myocardial infarction were confirmed (95.4% of reported cases). Time of onset of myocardial infarction was determined by reviews of hospital charts by a physician blinded to each subject's group assignment. These data reflect the participant's self-report of symptom onset time as described in the emergency room or attending physician's notes at the time of hospital entry. Time of onset of infarction was included in these analyses only if it could be determined within a 2-hour time interval. Using these criteria, information about time of onset was available in 211 cases (62%).

To evaluate the hypothesis that there is a circadian variation in the incidence of nonfatal myocardial infarction, the frequency of infarction occurring in consecutive 2-hour time intervals was plotted over a 24-hour cycle for all subjects as well as separately for physicians assigned to aspirin and to placebo. To evaluate the hypothesis that aspirin confers an augmented protective effect in the hours of awakening and assuming an upright posture, the percent reduction attributable to aspirin in the incidence of infarction was calculated for each time interval. In addition, for the 183 cases in which activity level at time of symptom onset was known, an analysis of the frequency of infarctions associated with sleep and recent awakening was performed.

$\chi^2$  tests for goodness of fit were used to test for differences in the frequency of infarctions between time intervals. In addition, for each analysis, the interval with the highest frequency was tested for a difference from the other time periods combined.



**FIGURE 1.** Distribution of the frequency of myocardial infarction (MI) onset among 211 participants in the Physicians' Health Study. The number of infarctions occurring in each 2-hour time interval is plotted for all subjects (Figure 1A), for subjects randomly selected for placebo therapy (Figure 1B), and for subjects randomly selected for aspirin therapy (Figure 1C). The 2-hour time interval around midnight is shown at both the 0-hour and 24-hour points.

## Results

Baseline characteristics of the participants in this study are presented in Table 1 according to treatment status. As expected in a randomized trial of this size, baseline cardiovascular risk profiles were virtually identical in the aspirin and placebo groups.

For all nonfatal myocardial infarctions, the frequency of symptom onset is distributed in a bimodal circadian variation with a primary peak frequency between 4:00 AM and 10:00 AM ( $p<0.001$ ) and a secondary smaller peak in the evening hours (Figure 1A). This variation is seen primarily in the placebo group ( $p<0.001$ ) (Figure 1B), while the aspirin group shows minimal circadian variation ( $p=0.16$ ) (Figure 1C). When these hourly distributions are directly compared, a difference in diurnal variation is apparent (Figure 2). Specifically, a marked blunting

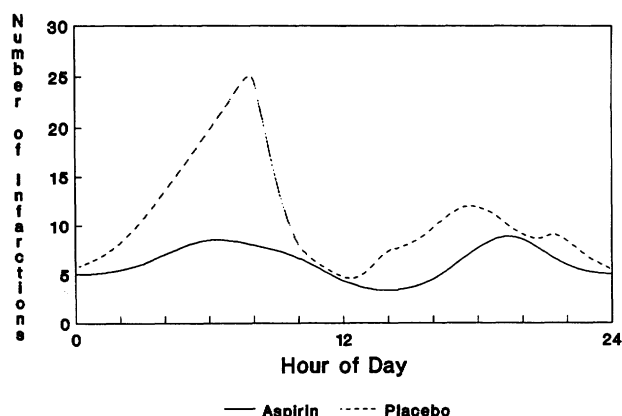


FIGURE 2. Graph of the estimated time and frequency of myocardial infarction onset among 11,034 subjects at risk in the aspirin group as compared to 11,037 subjects at risk in the placebo group. The 2-hour time interval around midnight is shown at both the 0-hour and 24-hour points.

of the morning primary peak is apparent in the aspirin group as compared with the placebo group. A net protective effect of aspirin throughout the 24-hour circadian cycle is also evident in this figure.

The overall reduction attributable to aspirin in the incidence of nonfatal infarction in this study sample is 44.8%. Figure 3 displays the magnitude of this reduction in 6-hour time intervals centered around 7:00 AM, the estimated mean time of awakening and rising from bed for the physicians participating in the study. Between the hours of 4:00 AM and 10:00 AM, aspirin is associated with a 59.3% reduction in the incidence of myocardial infarction as compared to a mean reduction of 34.1% for all other time periods combined ( $p[\text{one-tailed}]=0.053$ ). When classified by activity level, 26.2% of infarctions were reported by physicians to have awoken them from sleep and another 24.6% occurred within 3 hours of awakening. Figure 4 presents the distribution by percent of infarctions occurring while asleep and in successive 3-hour time intervals after awakening. The relative

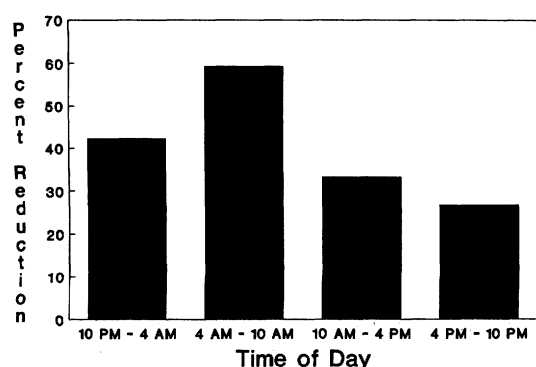


FIGURE 3. Distribution of the percent reduction attributable to aspirin therapy in the incidence of nonfatal myocardial infarction during different time periods of the day. Six-hour time intervals are centered around 7:00 AM, the estimated time of awakening for participants in the study.

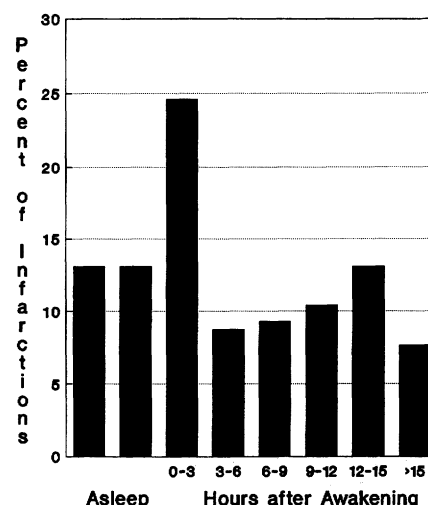


FIGURE 4. Distribution of the percent of myocardial infarctions occurring while asleep and in successive 3-hour intervals for infarcts with onset after awakening.

risk of infarction within 3 hours of awakening is nearly twice that of any other comparable period of the day ( $p<0.001$ ). These data were further analyzed by aspirin or placebo assignment. For infarcts occurring within 3 hours of rising, a 54.8% reduction in infarction is associated with aspirin therapy.

## Discussion

The present data indicate that for all cases of nonfatal myocardial infarction, there was a bimodal circadian variation in time of onset, with a primary peak in the waking hours and a secondary smaller peak in the evening. This result, produced in a homogenous study population of excellent medical historians, supports the findings of several earlier studies.<sup>1,2,12-21</sup> Further, an aspirin-associated reduction in the incidence of infarction appears throughout the circadian cycle. This finding is consistent with the role of platelet aggregation and thrombosis as a final event in the pathogenesis of infarction irrespective of any other triggering mechanism.<sup>22-24</sup> In addition, while a bimodal distribution of infarction onset is seen in the placebo group, the primary morning peak of infarction is substantially attenuated among participants randomly chosen to receive aspirin therapy. Specifically, there is an additional 25.2% protective effect associated with aspirin between 4:00 AM and 10:00 AM, the hours of awakening from sleep and assuming an upright posture. This protective effect appears to be particularly strong during the 3-hour time period occurring immediately after arising from a period of prolonged sleep. The timing and magnitude of this reduction closely corresponds to a previously reported 20% surge in platelet responsiveness to adenosine diphosphate associated with these activities.<sup>8</sup> This morning increase in platelet aggregation appears to be clinically important; in this trial, nearly one fourth of all infarctions occurred during this 3-hour high-risk period of the day.



Although these data indicate that aspirin blunts the circadian variation of acute myocardial infarction, there are some potential limitations that need to be considered in interpreting these findings. First, information about the time of symptom onset is available for 211 of the 342 physicians suffering nonfatal infarctions. This situation raises the question of a possible bias that could occur if those providing the information were systematically different from the total sample of cases. However, the 44.8% mean aspirin-associated reduction in the incidence of nonfatal infarction in our sample of 211 is comparable to the 41% reduction found for the 342 subjects suffering infarction in the Physicians' Health Study as a whole. This provides indirect but reassuring evidence against the existence of any major selection bias in our sample. Second, since serial standardized creatine kinase measurements in a core laboratory were not used to confirm the timing of infarction in this study, it is possible that a recall bias exists in describing time of onset of ischemic symptoms. This situation is unlikely among a study population of physicians, especially when previous studies have demonstrated an excellent correlation between patient-reported onset time and creatine kinase determinations.<sup>1,2</sup> Even if such a bias is present, the randomized, double-blind, placebo-controlled design of this trial makes it highly unlikely that there is a systematic difference in recalling ischemic onset time or activity level between the treatment groups. Finally, it is possible, at least in theory, that the observed lack of a statistically significant morning peak in the aspirin group is due merely to this group's smaller number of infarctions (75) rather than any true effect of the drug. This explanation seems unlikely because other studies have demonstrated circadian variation in cardiovascular disorders using population subsets as small as 56 and 32 patients.<sup>4,25</sup>

The current data offer several important insights into the pathophysiology of acute myocardial infarction. First, the bimodal daily distribution of infarction in this and earlier studies indicates that cardiac events do not occur randomly and suggests that an as yet unknown series of triggers may be important in the onset of infarction. While aspirin reduced the incidence of early morning infarction, it appears that this therapy did not reduce the evening second peak of infarction to the same degree. This finding adds support to the hypothesis that different myocardial triggers may be involved at different times of the day or in different types of infarction, a hypothesis consistent with the demonstration that there are altered circadian patterns of symptom onset for certain subgroups of patients, particularly those with non-Q wave infarction.<sup>26,27</sup> Second, the current data indicate that multiple factors are involved in triggering early-morning infarctions. Several investigators have suggested that the morning increase in the incidence of myocardial infarction is in part due to alterations in catecholamine state as reflected by morning

increases in systolic blood pressure<sup>28,29</sup> and epinephrine levels.<sup>8,30</sup> This concept is supported by the findings that  $\beta$ -blockers suppress the morning increase in the incidence of myocardial ischemia<sup>31</sup> and that patients on prior  $\beta$ -blocker therapy do not exhibit an increased incidence of morning myocardial infarction.<sup>2</sup> Other investigators, however, have also suggested a role for enhanced platelet aggregation in the triggering of early-morning infarction. Studies of platelet activation in response to adenosine diphosphate and epinephrine have shown that a surge in platelet aggregability occurs in the morning hours and may be related to waking from sleep and assuming an upright posture.<sup>7-9</sup> If critical periods of increased platelet aggregation exist, then treatment with low doses of aspirin, thereby inhibiting cyclooxygenase and preventing thromboxane formation,<sup>32</sup> may have an even greater role in the primary prevention of thrombosis during these early morning hours.

The findings in this paper support the hypothesis that increased platelet aggregation in the morning and upon arising contribute to the occurrence of nonfatal myocardial infarction and that aspirin may reduce the risk of infarction by protecting against platelet aggregation during critical periods of the day. Moreover, our finding that nearly 25% of all infarctions occurred within 3 hours of awakening suggests that specific activities, as well as time of day, may be important in the onset of acute ischemia. These findings, together with those from previous studies of circadian variation, support the hypothesis that several physiological changes or triggering events are involved in the onset of infarction. These triggers, whether they be periods of hypercoagulability, relative exercise intolerance, or catecholamine surges, may constitute short-term risk factors for coronary occlusion in much the same way that hypertension, smoking, and elevated cholesterol levels constitute long-term risk factors for cardiovascular disease. Other daily cyclical changes, such as those in plasma cortisol<sup>30,33</sup> and endogenous fibrinolytic activity,<sup>34,35</sup> are also likely to be involved in this triggering process.

The evolving theory that short-term risks or triggers are involved in the onset of acute myocardial infarction has important implications for future research. To date, the incidence of myocardial infarction has been reduced by interventions on long-term risk factors such as elevated blood pressure, elevated cholesterol levels, and cigarette smoking. While these long-term risk reductions remain critical in decreasing the risk of cardiovascular disease, interventions aimed at short-term determinants of thrombosis may also prove important in reducing the risk of sudden coronary occlusion. This randomized trial of alternate-day aspirin intake suggests that short-term precipitants of infarction, once elucidated, may be amenable to specific therapy or intervention. Analyzing the effect of a therapeutic agent on the circadian variation of the incidence of myocardial infarction is one way to elucidate such acute precipitants of

infarction as well as a mechanism to evaluate potential interventions. Further use of this technique in trials employing a randomized placebo-controlled design may lead to additional strategies in the primary prevention of myocardial infarction.

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