JACC: CARDIOVASCULAR INTERVENTIONS VOL. 4, NO. 2, 2011

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2010.09.025

Circadian Variation in Coronary Stent Thrombosis

Karim D. Mahmoud, BSc,*† Ryan J. Lennon, MS,‡ Henry H. Ting, MD, MBA,*§ Charanjit S. Rihal, MD, MBA,* David R. Holmes, Jr, MD*

Rochester, Minnesota; and Groningen, the Netherlands

Objectives We sought to determine the circadian, weekly, and seasonal variation of coronary stent thrombosis.

Background Other adverse cardiovascular events such as acute myocardial infarction are known to have higher incidences during the early morning hours, Mondays, and winter months.

Methods The Mayo Clinic Percutaneous Coronary Intervention Registry was searched for patients admitted to our center who underwent repeat percutaneous coronary intervention in a previously stented coronary artery segment. Stent thrombosis was confirmed by angiographic review, and date and time of symptom onset were obtained from medical records.

Results We identified 124 patients with definite stent thrombosis and known date and time of symptom onset. In these patients, onset of stent thrombosis was significantly associated with time of day ($p = 0.006$), with a peak incidence around 7:00 AM. When patients were subdivided into early stent thrombosis (0 to 30 days; $n = 49$), late stent thrombosis (31 to 360 days; $n = 30$), and very late stent thrombosis (>360 days; $n = 45$), only early stent thrombosis remained significantly associated with time of day ($p = 0.030$). No association with the day of the week was found ($p = 0.509$); however, onset of stent thrombosis did follow a significant seasonal pattern, with higher occurrences in the summer ($p = 0.036$).

Conclusions Coronary stent thrombosis occurs more often in the early morning hours. Early stent thrombosis follows a circadian rhythm with a peak at 7:00 AM. This pattern was not significant in late and very late stent thrombosis. Occurrences throughout the week were equally distributed, but stent thrombosis was more likely to occur in the summer months. (J Am Coll Cardiol Intv 2011;4: 183–90) © 2011 by the American College of Cardiology Foundation

From the *Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; †Groningen International Program of Science in Medicine GIPS-M, University of Groningen, Groningen, the Netherlands; ‡Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; and the §Knowledge and Encounter Research Unit, Mayo Clinic, Rochester, Minnesota. Mr. Mahmoud has the following grant sponsors: Netherlands Heart Foundation, Groningen University Fund, Marco Polo Fund, and the Jan Kornelis de Kock Foundation. All other authors have reported that they have no relationships to disclose.

Manuscript received June 22, 2010; revised manuscript received July 30, 2010, accepted September 3, 2010.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 2, 2011
FEBRUARY 2011:183–90

Twenty-four-hour (circadian) patterns are present in numerous physiological processes. Circadian variation with a morning peak has been found in heart rate, blood pressure, (1,2) and levels of multiple hormones such as renin, aldosterone, and cortisol (3,4). It is becoming increasingly clear that adverse events follow circadian patterns as well. Circadian variation with a peak in the morning has been observed in stroke (5), unstable angina pectoris (6), acute myocardial infarction (AMI) (7,8), and sudden cardiac death (7,9). In addition, weekly patterns with a peak on Monday and seasonal patterns with a peak in the winter have been reported in AMI (10–12) and sudden cardiac death (13,14). Most of these temporal patterns seem to be attributable to triggering factors, such as hemodynamic and hemostatic changes, physical exertion, and mental stress (15–18).

In theory, it is likely that coronary stent thrombosis also follows a circadian pattern, due to an increased tendency toward thrombosis in the morning hours (18–20). However, this hypothesis has only been confirmed by 1 report with a sample size of 21 patients (21). Furthermore, the role of triggering factors in stent thrombosis onset has been suggested in a case report (22). More insight in patterns of onset of stent thrombosis and potential triggers might help to prevent stent thrombosis by optimizing medical treatment during high-risk intervals throughout the day, week, and year.

Abbreviations and Acronyms

AMI = acute myocardial infarction
IQR = interquartile range
MET = metabolic equivalent
PCI = percutaneous coronary intervention

To address the hypothesis that stent thrombosis follows a circadian pattern, we performed an analysis of the Mayo Clinic Percutaneous Coronary Intervention Registry. Second, we assessed weekly and seasonal patterns and characterized potential triggering events preceding stent thrombosis onset.

Methods

Study design. After obtaining institutional review board approval, a retrospective analysis was performed, with the Mayo Clinic Percutaneous Coronary Intervention Registry. This database includes baseline, procedural, angiographic, and outcome data on all patients undergoing percutaneous coronary intervention (PCI) at the Mayo Clinic, Rochester, Minnesota. For this registry, data are prospectively collected by experienced interventional cardiology data technicians. The database supervisor performs routine audits of 10% of the records for quality control purposes. We identified patients admitted to our center who had undergone a repeated PCI procedure in a coronary artery segment where a stent had been previously placed and who had experienced sudden onset or worsening of anginal symptoms within 1 week of this repeated PCI procedure. The later criterion was determined by medical record review. We excluded patients with unknown symptom onset date and time and patients who had previously declined to have their medical records reviewed for research, as is required by Minnesota state law. We did not study patients with sudden death, because angiographic evidence of stent thrombosis could not be obtained in these patients. Subsequently, angiograms of eligible study subjects were reviewed for angiographic evidence of stent thrombosis by experienced interventional cardiology trainees blinded to the primary outcome of this study. Thus, the subjects we identified by means of this method have definite stent thrombosis according to the Academic Research Consortium definition: "an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion" (23). In addition, medical records were reviewed for level of physical activity before symptom onset, and other events that had potentially triggered stent thrombosis were identified.

Definitions. In accordance with the Academic Research Consortium definition, stent thrombosis was subdivided into early stent thrombosis (0 to 30 days), late stent thrombosis (31 to 360 days), and very late stent thrombosis (>360 days) (23). Multivessel disease was defined as the number of vessels wherein the first had at least 70% stenosis and subsequent vessels had at least 50% stenosis. For the index procedure (initial stent placement), lesion dissection was defined as the presence of an intimal tear during the procedure, regardless of its persistence after completion of the procedure; and stent size was defined as the smallest diameter of any stent placed in the coronary artery segment where stent thrombosis would later occur. Finally, arterial calcification and lesion calcification were defined as any visible calcium during coronary angiography. The level of physical activity before stent thrombosis symptom onset was graded with metabolic equivalents (METs). One MET was defined as the energy spent/minute by a subject sitting quietly and is equivalent to 3.5 ml of oxygen uptake/kilogram of body weight/minute by a 70-kg adult (15). This method has previously been used in studies assessing physical activity as a potential trigger of myocardial infarction (15,17). We defined the categories: sleeping (1 MET), lying or sitting (1 to 2 METs), light to moderate exertion (3 to 5 METs), and heavy exertion (≥6 METs). Furthermore, we reviewed medical records for other potential triggers of stent thrombosis. This included documented medication noncompliance and patients who were initially admitted to our center for other medical conditions but developed stent thrombosis during their hospital stay. Patients who were admitted for stent thrombosis but were found to have other important medical conditions at admission (e.g., infection) were also considered to have a potential triggering factor for stent thrombosis.

Statistical analysis. Continuous variables are summarized as mean ± SD, unless otherwise specified. Discrete variables are presented as fractions and percentages. Group differ-

ences for categorical variables were tested with Pearson chi-square test. The distribution of time of symptom onset over the 24-h clock, week, and year were tested against the null hypothesis of a uniform likelihood with the Rayleigh test (24). For weekly and seasonal patterns, hour of week and day of year were used, respectively. To help identify the average temporal trends, sinusoidal functions were used to model stent thrombosis as functions of the time of symptom onset over the day, week, and year. The 4 degrees of freedom sinusoid consisted of 1-period cosine, 1-period sine, 2-period cosine, and 2-period sine variables. A 2-tailed p value <0.05 was considered significant. All analyses were conducted with SAS 9.1.3 and JMP 8.0 (SAS Institute, Cary, North Carolina).

Results

Patient population. One thousand six hundred thirty-one patients with a repeat intervention in a previously stented coronary artery segment were identified. In 252 patients, the onset of ischemic symptoms was within 1 week of intervention, and symptom onset date and time could be obtained from the medical record. After angiographic review, 124 patients with definite stent thrombosis were identified. The other patients were found to have restenosis rather than stent thrombosis. Index procedures were performed between February 21, 1995 and June 23, 2009. Subsequent procedures for stent thrombosis were performed between February 22, 1995 and August 20, 2009. Baseline clinical and procedural characteristics at the time of the index procedure are shown in Table 1. Unless otherwise specified, the procedural data relate to the coronary artery segment where stent thrombosis would later occur. Note that 33% of patients were diabetic, 19% of patients had peripheral vascular disease, and 15% of patients had an ongoing malignancy or a history of malignancy in the past 5 years. Furthermore, after the index procedure, dissection of the coronary artery segment where stent thrombosis would later occur was present in 16% of patients.

Temporal variation. Stent thrombosis occurred after a median of 97 days of initial stent placement, with an interquartile range (IQR) of 4 to 862 days. The patient sample included 49 patients with early stent thrombosis (median 3 days after index procedure; IQR: 1 to 5 days), 30 patients with late stent thrombosis (median 116 days; IQR: 77 to 216 days), and 45 patients with very late stent thrombosis (median 38 months; IQR: 26 to 63 months).

The primary outcome, stent thrombosis as a function of 24-h circadian time, is shown in Figure 1. We found a significant association between the onset of stent thrombosis and time of day, with a low incidence at approximately 8:00 PM and a peak at approximately 7:00 AM ($p = 0.006$). However, when patients were subdivided into early, late, and very late stent thrombosis, only the association between

Table 1. Patient Characteristics During Index Procedure (n = 124)

Clinical	
Age (yrs)	62.7 ± 13.4
Male	88/124 (71)
Body mass index (kg/m^2)	29.5 ± 5.4 (n = 123)
Systolic blood pressure (mm Hg)	126.6 ± 26.7 (n = 60)
Heart rate (beats/min)	69.5 ± 12.4 (n = 60)
Hypertension	83/115 (72)
Hypercholesterolemia	93/116 (80)
Diabetes	40/121 (33)
Current smoker	39/119 (33)
CHF on presentation	13/113 (12)
Peripheral vascular disease	22/118 (19)
Malignancy	18/119 (15)
Metastatic malignancy	2/119 (1.7)
Family history of CAD	37/83 (45)
Prior PTCA	46/124 (37)
Prior myocardial infarction	
Single	60/121 (50)
Multiple	27/121 (22)
Prior coronary artery bypass grafting	36/121 (30)
Procedural	
Pre-procedural TIMI flow grade	
0	13/86 (15)
1	4/86 (4.7)
2	8/86 (9.3)
3	61/86 (71)
Procedure-related vessel*	
Left anterior descending artery	40/124 (32)
Right coronary artery	41/124 (33)
Left circumflex artery	23/124 (19)
Left main artery	4/124 (3.2)
Vein graft	19/124 (15)
Bifurcation lesion	14/108 (13)
Calcium in stenosis	27/98 (28)
Calcium in artery	34/90 (38)
Dissection	18/114 (16)
Post-procedural TIMI flow grade	
2	3/111 (2.7)
3	108/111 (97)
Stent	
Type of stent	
Drug-eluting stent	45/124 (36)
Bare-metal stent	79/124 (64)
Stent diameter (mm)	3.2 ± 0.6 (n = 123)
Total number of stents	
1	65/124 (52)
2	38/124 (31)
>2	21/124 (17)

All procedural and stent data relate to the coronary artery segment where stent thrombosis would later occur, except "total number of stents," which relates to the index procedure as a whole. Values are mean ± SD or n/total n (%). *Total % is >100%, because 3 patients had stent thrombosis in 2 vessels.

CAD = coronary artery disease; CHF = congestive heart failure; PTCA = percutaneous transluminal coronary angioplasty; TIMI = Thrombolysis In Myocardial Infarction.

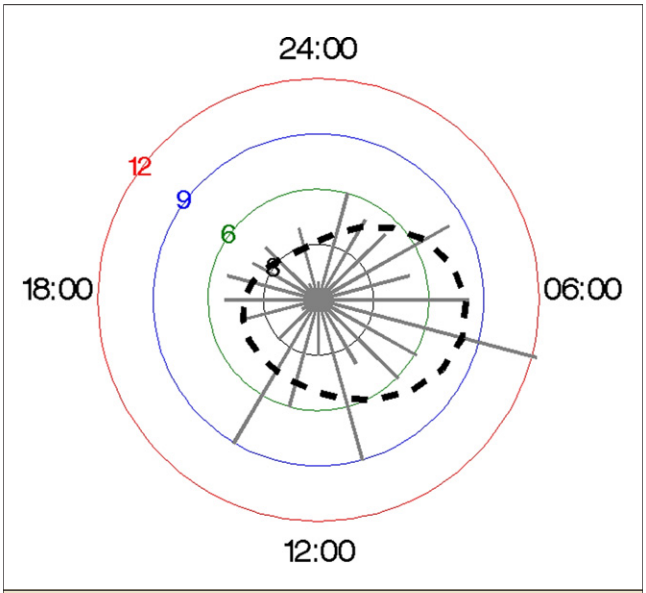

Figure 1. Circadian Variation of Overall Stent Thrombosis (n = 124)

The **spokes** are drawn from the center of the circle to the number of stent thrombosis events that occurred that hour of the day; the **spoke angles** represent the time of day (rounded to the nearest hour). The scale is presented by concentric circles; the **center of the circles** represents 0 frequency; and the **outer circle** represents 12 stent thrombosis events. The **dashed line** is a sinusoidal smoothing function indicating the average circadian trends. The plot indicates that there was a low incidence of stent thrombosis at approximately 7:00 PM to 12:00 AM and a peak incidence at approximately 7:00 AM. The association between onset of stent thrombosis and time of day was significant (p = 0.006).

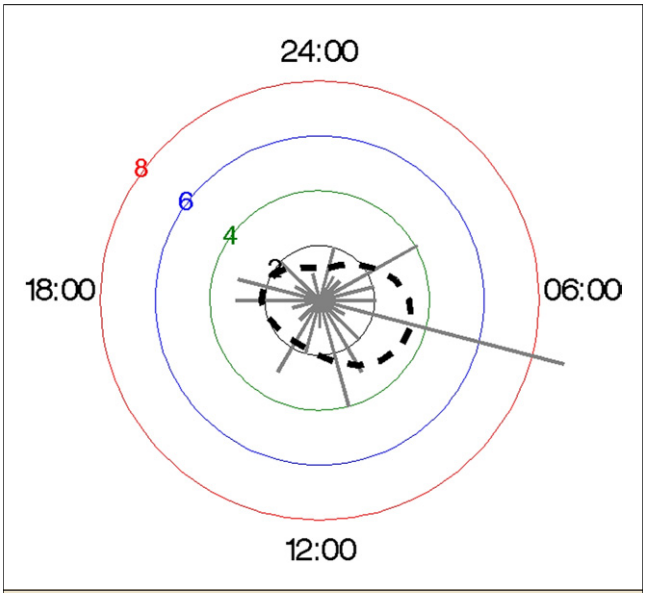

Figure 2. Circadian Variation of Early Stent Thrombosis (n = 49)

An explanation of the figure is provided in the legend of Figure 1. The plot shows a significant association between early stent thrombosis and time of day (p = 0.030). A peak can be appreciated at approximately 7:00 AM.

early stent thrombosis and time of day remained significant (p = 0.030, p = 0.537, and p = 0.096, respectively) (Figs. 2–4). No significant association between stent thrombosis symptom onset and day of week was found (p = 0.509). When looking at seasonal patterns, there were higher stent thrombosis rates in the summer months, with a peak occurrence between the end of July and the beginning of August (p = 0.036) (Fig. 5).

Procedure indication and medication use. Pre-procedural medication use and indication for the index and stent thrombosis procedures are presented in Table 2. Two-thirds of the patients with stent thrombosis presented with myocardial infarction, most commonly ST-segment elevation myocardial infarction. Overall, 96% of patients were taking aspirin at the time of stent thrombosis. Approximately 89% of patients with early stent thrombosis were taking clopidogrel or ticlopidine, but less than one-half of the patients with late or very late stent thrombosis used these medications. When subdivided by type of stent, 86% of patients with a bare-metal stent and early stent thrombosis were using clopidogrel or ticlopidine before onset of stent thrombosis. This rate was 7 of 20 (35%) for patients with a bare-metal stent and late stent thrombosis and 6 of 25 (24%) for patients with a bare-metal stent and very late stent thrombosis. In patients with a drug-eluting stent, 14 of 15 patients (93%) presenting with early stent thrombosis were using clopidogrel (none of the patients were taking ticlopidine). This rate was only 6 of 10 (60%) for patients with a drug-eluting stent and late stent thrombosis and 8 of 20 (40%) in patients with a drug-eluting stent and very late stent thrombosis.

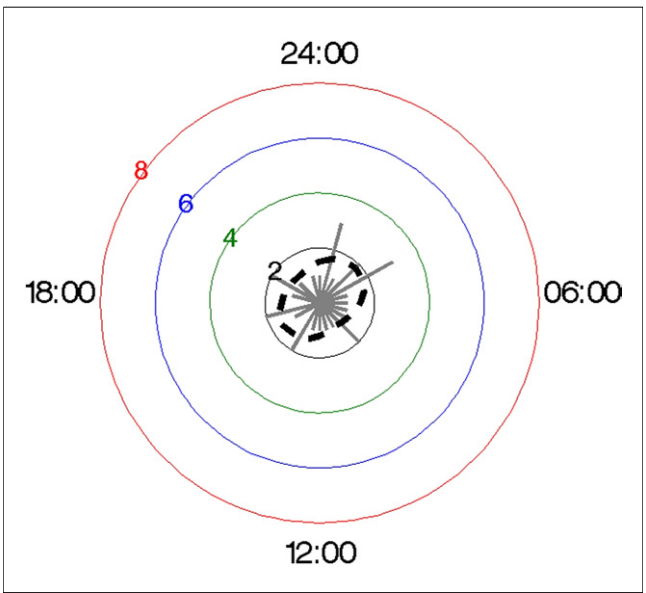

Figure 3. Circadian Variation of Late Stent Thrombosis (n = 30)

An explanation of the figure is provided in the legend of Figure 1. No significant association between late stent thrombosis and time of day was found (p = 0.537).

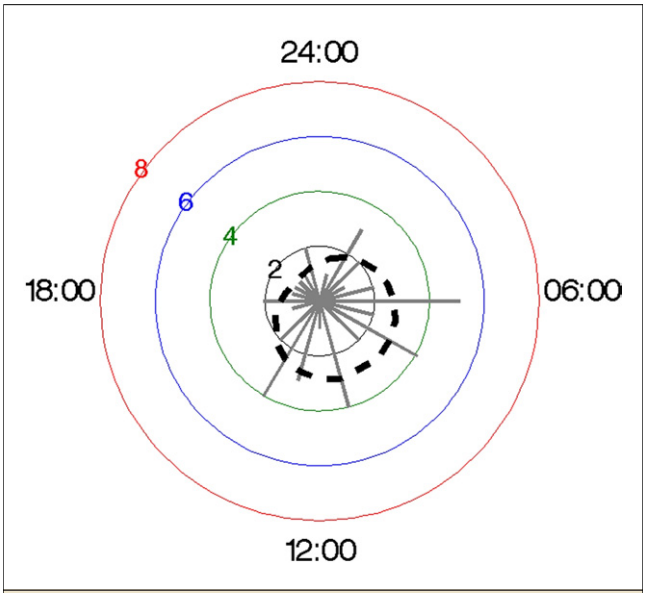

Figure 4. Circadian Variation of Very Late Stent Thrombosis (n = 45)

An explanation of the figure is provided in the legend of Figure 1. No significant association between very late stent thrombosis and time of day was found (p = 0.096). There was, however, a trend toward a higher incidence of stent thrombosis between 6:00 AM and 12:00 PM.

Potential triggers. In 62 patients, activity level before stent thrombosis symptom onset was documented in their medical record. Twenty-one (33.9%) patients were sleeping (1 MET), 16 (25.8%) patients were lying or sitting (1 to 2 METs), 18 (29.0%) patients were engaged in light-to-moderate physical exertion (3 to 5 METs), and 7 (11.3%) patients were engaged in heavy physical exertion (≥6 METs). We did not find significant differences in physical activity level among patients with early, late, and very late stent thrombosis. Furthermore, we identified other medical conditions that might have triggered stent thrombosis. These are presented in Table 3. In 5.6% of patients, medication noncompliance was explicitly documented. Furthermore, 4% of patients were hospitalized for surgery or invasive diagnostics and developed stent thrombosis during this hospital stay. Finally, it is important to note that 4% of patients were found to have either pneumonia or a urinary tract infection at admission to our center.

Discussion

Although the incidence of stent thrombosis decreased in recent years due to dual antiplatelet therapy and improved stent design, the consequences of stent thrombosis are often severe. Most patients that experience stent thrombosis die or suffer AMI (25). In the present study, we demonstrated on a continuous scale that stent thrombosis follows a circadian rhythm with a peak at 7:00 AM. This circadian rhythm might be absent or less-pronounced in late and very late stent thrombosis. Furthermore, we found a significant association between stent thrombosis and season with a peak in the summer months. No weekly pattern in stent thrombosis onset was found.

Several physiological processes might contribute to the increased incidence of stent thrombosis in the morning. First, renin-angiotensin-aldosterone system activity is increased between 6:00 AM and 8:00 AM, (3) thus causing higher blood pressure and heart rate in the morning (1,2). This might trigger stent thrombosis by causing shear stress. Second, blood viscosity tends to be higher in the morning, and this might be magnified by assuming the upright posture after a night of supine sleep (26). Higher blood viscosity in combination with higher vascular tone (27) makes the occurrence of symptomatic stent thrombosis more likely in the morning. Third, patients might have suffered from coronary spasm, which has been associated with thrombus formation (28) and mainly occurs during the night and in the morning (29). Fourth, a hypercoagulable and hypofibrinolytic state might be responsible for the morning excess in cardiovascular events. Tofler et al. (20) reported increased platelet aggregability. Furthermore, Andreotti et al. (19) demonstrated that tissue-type plasminogen activator, the major component of the fibrinolytic system, was reduced in the morning, reaching lowest values at 6:00 AM. At the same time, the activity of the fast-acting inhibitor of fibrinolysis, plasminogen activator inhibitor, was increased. Finally, antithrombotic medication such as aspirin, clopidogrel, and ticlopidine are likely to have nadir

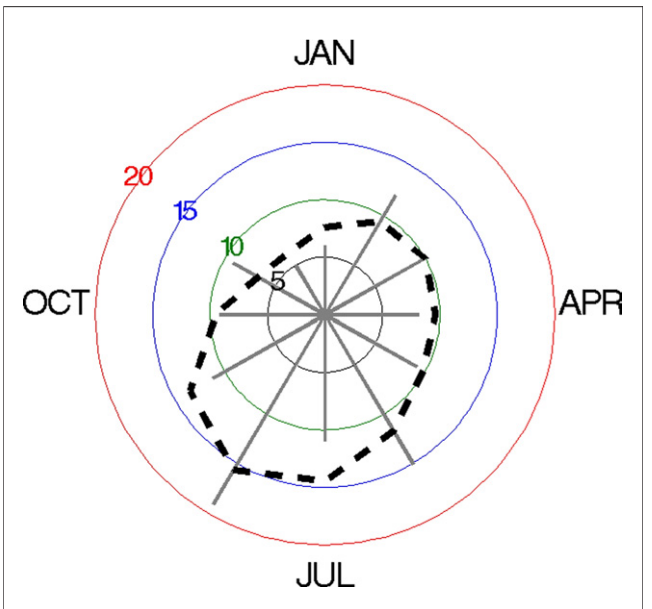

Figure 5. Incidence of Stent Thrombosis Throughout the Year (n = 124)

There was a significant association between stent thrombosis onset and day of year (p = 0.034). Higher rates of stent thrombosis were found in the summer months, reaching peak incidences in July and August.

Table 2. Indication for the Procedure and Pre-Procedural Medication Use

		Stent Thrombosis			
	Index Procedure (n = 124)	Early (n = 49)	Late (n = 30)	Very Late (n = 45)	p Value
Indication for the procedure					
Unstable angina	65/124 (52)	19/49 (39)	15/30 (50)	5/45 (11)	
STEMI	28/124 (23)	23/49 (47)	11/30 (37)	27/45 (60)	
NSTEMI	18/124 (15)	6/49 (12)	3/30 (10)	12/45 (27)	
Positive exercise test	6/124 (4.8)		1/30 (3.3)		
Arrhythmia	1/124 (0.8)	1/49 (2.0)		1/45 (2.2)	
Chronic heart failure	2/124 (1.6)				
Asymptomatic	1/124 (0.8)				
Other	3/124 (2.4)				
Pre-procedural medication					
Aspirin	113/118 (96)	48/48 (100)	29/30 (97)	41/45 (91)	0.968
Beta blocker	101/119 (85)	41/48 (85)	24/29 (83)	39/45 (87)	0.978
Clopidogrel	29/105 (28)	34/44 (77)	13/30 (43)	14/45 (31)	0.0001
Ticlopidine	3/119 (2.5)	5/44 (11)			0.494
Anticoagulant	4/118 (3.4)	7/49 (14)	1/29 (3.5)	1/45 (2.2)	0.254

Values are n/total n (%). The p values are index procedure versus overall stent thrombosis procedure.
NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

levels in the morning, just before the patient wakes up and takes a new dose.

Our study confirms a previous report on circadian variation in stent thrombosis. To our knowledge, there has only been 1 prior study that assessed circadian variation of stent thrombosis in a group of 21 patients (21). Tamura et al. found a higher morning incidence of subacute stent thrombosis in patients with a bare-metal stent. However, this study used 6-h intervals and did not assess weekly and seasonal patterns due to a limited sample size.

In addition to a circadian variation, we found a higher occurrence of stent thrombosis in the summer months. An intuitive explanation might be that patients were more active in the warm months of the year compared with the cold months. However, most reports assessing seasonal patterns in AMI find higher incidences in the winter months (10,11). Still, even passive heating in the summer can cause sympathetic nervous system activation and increased heart rate and thus might explain higher stent thrombosis rates in the summer (30,31).

Table 3. Potential Triggers and Risk Factors for Stent Thrombosis (n = 124)

Pharmacological triggers	
Medication noncompliance	7/124 (5.6)
Hospital admission for other problems	
Surgery/invasive diagnostics	5/124 (4.0)
Pneumonia*	4/124 (3.2)
Current chemotherapy/radiotherapy	2/124 (1.6)
Urinary tract infection	1/124 (0.8)
Pulmonary embolism	1/124 (0.8)
Stroke	1/124 (0.8)
Onset during hemodialysis	1/124 (0.8)
Onset during adenosine sestamibi	1/124 (0.8)
Factor V Leiden	3/124 (2.4)
History of chest radiation	1/124 (0.8)
Total potential triggers/risk factors†	27
Number of patients with potential triggers/risk factors	26/124 (21)

Values are n/total n (%). *1 being possible pneumonia; †1 patient had 2 potential triggers.

We did not find a significant association between onset of stent thrombosis and day of the week. In other cardiovascular conditions, such as AMI, higher occurrences have been found on Monday (11,12). It is likely that mental stress accounts for this pattern, because it is less pronounced in the nonworking population. The absence of this pattern in stent thrombosis might suggest a more limited role of mental stress as a triggering factor for stent thrombosis.

When we looked at the baseline characteristics of our patients, high rates of diabetes, peripheral vascular disease, malignancy, and dissection were found. These conditions have been shown to be independent risk factors for stent thrombosis in a study by van Werkum et al. (32). We tried to establish physical activity level and other potential triggers for stent thrombosis onset, in addition to these data. Although there is a great body of evidence with regard to the role of triggers in onset of AMI and sudden cardiac death, this is not the case for stent thrombosis. We had several important findings. First, we found that stent thrombosis was preceded by heavy physical exertion in 11.3% of patients. Most patients, however, were either asleep or performing light exercise. In a recent report describing 3 cases of stent thrombosis, the association with

physical exertion was suggested (22). Our results show that there is indeed circumstantial evidence that heavy physical exertion might play a role in stent thrombosis onset. Surely, it is unlikely that 11% of a population is engaged in heavy physical activity at a certain point. More research on this topic is warranted to confirm our findings and estimate the size of this risk factor. Previous studies using the case-crossover design have identified heavy physical exertion as a risk factor for AMI (15,17). Second, 4% of patients were hospitalized for surgery or invasive diagnostics. These conditions might have interfered with the antithrombotic medication regimen, thus causing stent thrombosis. Third, in 5.6% of patients, medication noncompliance was explicitly documented. However, we found that a much larger proportion of patients did not use clopidogrel or ticlopidine for at least 30 days (2007 guideline) or 1 year (current guideline) after implantation of a bare-metal stent or for at least 1 year after implantation of a drug-eluting stent, as is recommended by the American College of Cardiology/American Heart Association guidelines (33,34). Fourth, approximately 4% of patients had an ongoing acute infection before stent thrombosis onset. Acute infections, particularly in the respiratory and urinary tract, might well be triggers of stent thrombosis, because they have shown to increase the risk of other adverse cardiovascular events as well (35–37). For instance, a large study in the U.K. demonstrated an increased risk of AMI and stroke in patients with a respiratory tract infection (including pneumonia) or a urinary tract infection (36). Finally, we found factor V Leiden in 2.4% of our patients. Although factor V Leiden is a well-known risk factor for venous thrombosis, we did not find a higher prevalence of this condition in our patient sample compared with the general population (approximately 6%) (38,39). In addition, multiple reports have suggested that factor V Leiden is not associated with arterial thrombosis (38,40).

Study limitations. Given the number of theoretical mechanisms for circadian rhythms but the modest number of patients reported, analysis of associations must be regarded as speculative. Although we used prospectively collected data, this was a retrospective analysis. Because date and time of symptom onset were unavailable in some patients, our sample does not consist of consecutive patients. Also, data availability did not allow us to identify patients who had undergone a single index or stent thrombosis procedure at our center and the other procedure at another center. However, we believe lack of data was completely random and was unlikely to have biased our analysis. Furthermore, because stent thrombosis is a relatively rare complication, our sample size was limited. Therefore, this study might not have had enough statistical power to demonstrate circadian variation in late and very late stent thrombosis. That we did not find a weekly pattern could also be due to limited power. Another limitation is that we did not study patients with sudden death. We recognize that stent thrombosis often leads to death (25), but we chose not to include these patients, because angiographic evidence of stent thrombosis could not be obtained. Another reason is that the well-established circadian rhythm of sudden cardiac death (7,9) would pose a potential source of bias in our analysis. However, exclusion of sudden deaths might account for the remarkable seasonal distribution we found. It might be possible that stent thrombosis is more severe during the winter and thus causes more sudden deaths. Finally, we did not include a control group in our analysis of potential triggers of stent thrombosis. Therefore, statements made regarding potential triggers could not be tested, and this part of our analysis should be seen as merely explorative.

Conclusions

This study shows that: 1) stent thrombosis follows a circadian rhythm with an early morning peak; 2) stent thrombosis follows a seasonal rhythm with a peak in the summer; and 3) potential triggers of stent thrombosis can be identified in a considerable number of patients—mainly exercise and conditions or behavior that interfere with an optimal medication regimen.

Acknowledgments

The authors thank the interventional cardiology fellows Drs. Jeff Booker, Farhan Khawaja, Sridevi Pitta, Inder Singh, and Prasanna Venkatesh Kumar for their help with the angiographic review.

Reprint requests and correspondence: Dr. David R. Holmes, Jr, Department of Cardiovascular Diseases, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905. E-mail: holmes.david@mayo.edu.

REFERENCES

1. Giles T. Relevance of blood pressure variation in the circadian onset of cardiovascular events. J Hypertens Suppl 2005;23:S35–9.
2. Hermida RC, Ayala DE, Fernández JR, Mojón A, Alonso I, Calvo C. Modeling the circadian variability of ambulatorily monitored blood pressure by multiple-component analysis. Chronobiol Int 2002;19:461–81.
3. Portaluppi F, Bagni B, degli Uberti E, et al. Circadian rhythms of atrial natriuretic peptide, renin, aldosterone, cortisol, blood pressure and heart rate in normal and hypertensive subjects. J Hypertens 1990;8:85–95.
4. Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab 1971;33:14–22.
5. Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. Stroke 1998;29:992–6.
6. Cannon CP, McCabe CH, Stone PH, et al. Circadian variation in the onset of unstable angina and non-Q-wave acute myocardial infarction (the TIMI III Registry and TIMI IIIB). Am J Cardiol 1997;79:253–8.
7. Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 1997;79:1512–6.

8. Muller JE, Stone PH, Turi ZG, et al. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315–22.
9. Arntz HR, Willich SN, Oeff M, et al. Circadian variation of sudden cardiac death reflects age-related variability in ventricular fibrillation. Circulation 1993;88:2284–9.
10. Spencer FA, Goldberg RJ, Becker RC, Gore JM. Seasonal distribution of acute myocardial infarction in the second National Registry of Myocardial Infarction. J Am Coll Cardiol 1998;31:1226–33.
11. Spielberg C, Falkenhahn D, Willich SN, Wegscheider K, Völler H. Circadian, day-of-week, and seasonal variability in myocardial infarction: comparison between working and retired patients. Am Heart J 1996;132:579–85.
12. Willich SN, Löwel H, Lewis M, Hörmann A, Arntz HR, Keil U. Weekly variation of acute myocardial infarction. Increased Monday risk in the working population. Circulation 1994;90:87–93.
13. Witte DR, Grobbee DE, Bots ML, Hoes AW. A meta-analysis of excess cardiac mortality on Monday. Eur J Epidemiol 2005;20:401–6.
14. Kloner RA, Poole WK, Perritt RL. When throughout the year is coronary death most likely to occur? A 12-year population-based analysis of more than 220 000 cases. Circulation 1999;100:1630–4.
15. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE, Determinants of Myocardial Infarction Onset Study Investigators. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. N Engl J Med 1993;329:1677–83.
16. Tofler GH, Muller JE. Triggering of acute cardiovascular disease and potential preventive strategies. Circulation 2006;114:1863–72.
17. Willich SN, Lewis M, Löwel H, Arntz HR, Schubert F, Schröder R. Physical exertion as a trigger of acute myocardial infarction. N Engl J Med 1993;329:1684–90.
18. Montagnana M, Salvagno GL, Lippi G. Circadian variation within hemostasis: an under-recognized link between biology and disease? Semin Thromb Hemost 2009;35:23–33.
19. Andreotti F, Davies GJ, Hackett DR, et al. Major circadian fluctuations in fibrinolytic factors and possible relevance to time of onset of myocardial infarction, sudden cardiac death and stroke. Am J Cardiol 1988;62:635–7.
20. Tofler GH, Brezinski D, Schafer AI, et al. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 1987;316:1514–8.
21. Tamura A, Watanabe T, Nagase K, et al. Circadian variation in symptomatic subacute stent thrombosis after bare metal coronary stent implantation. Am J Cardiol 2006;97:195–7.
22. Zwart B, Van Kerkvoorde TC, Van Werkum JW, Breet NJ, Ten Berg JM, Van't Hof AW. Vigorous exercise as a triggering mechanism for late stent thrombosis: a description of three cases. Platelets 2010;21:72–6.
23. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9.
24. Wilkie D. Rayleigh test for randomness of circular data. Appl Statist 1983;32:311–2.
25. Orford JL, Lennon R, Melby S, et al. Frequency and correlates of coronary stent thrombosis in the modern era: analysis of a single center registry. J Am Coll Cardiol 2002;40:1567–72.
26. Thrall G, Lane D, Carroll D, Lip GY. A systematic review of the prothrombotic effects of an acute change in posture: a possible mechanism underlying the morning excess in cardiovascular events? Chest 2007;132:1337–47.
27. Quyyumi AA, Panza JA, Diodati JG, Lakatos E, Epstein SE. Circadian variation in ischemic threshold. A mechanism underlying the circadian variation in ischemic events. Circulation 1992;86:22–8.
28. Oshima S, Yasue H, Ogawa H, Okumura K, Matsuyama K. Fibrinopeptide A is released into the coronary circulation after coronary spasm. Circulation 1990;82:2222–5.
29. Kawano H, Motoyama T, Yasue H, et al. Endothelial function fluctuates with diurnal variation in the frequency of ischemic episodes in patients with variant angina. J Am Coll Cardiol 2002;40:266–70.
30. Crandall CG, Zhang R, Levine BD. Effects of whole body heating on dynamic baroreflex regulation of heart rate in humans. Am J Physiol Heart Circ Physiol 2000;279:H2486–92.
31. Yamamoto S, Iwamoto M, Inoue M, Harada N. Evaluation of the effect of heat exposure on the autonomic nervous system by heart rate variability and urinary catecholamines. J Occup Health 2007;49:199–204.
32. van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol 2009;53:1399–409.
33. King SB III, Smith SC Jr., Hirshfeld JW Jr., et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;51:172–209.
34. Kushner FG, Hand M, Smith SC Jr., et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54:2205–41.
35. Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. Eur Heart J 2008;29:96–103.
36. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;351:2611–8.
37. Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. Lancet 1998;351:1467–71.
38. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med 1995;332:912–7.
39. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. JAMA 1997;277:1305–7.
40. Marcucci R, Brogi D, Sofi F, et al. PAI-1 and homocysteine, but not lipoprotein (a) and thrombophilic polymorphisms, are independently associated with the occurrence of major adverse cardiac events after successful coronary stenting. Heart 2006;92:377–81.

Key Words: angioplasty ■ circadian rhythm ■ seasons ■ stents ■ thrombosis.