European Journal of Epidemiology (2005) 20: 401–406
DOI 10.1007/s10654-004-8783-6
© Springer 2005

A meta-analysis of excess cardiac mortality on monday

D.R. Witte, D.E. Grobbee, M.L. Bots & A.W. Hoes
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Accepted in revised form 22 November 2004

Abstract. *Background*: Available evidence suggests a peak in the incidence of cardiovascular events on Mondays compared to other days of the week. The exact magnitude of the excess risk and the role of age and gender, however, remain unclear. *Objective*: To quantify the excess risk associated with the Monday peak in cardiovascular mortality and to explore the role of age and gender. *Methods*: A meta-analysis of available published studies reporting on weekly patterns in incidence of myocardial infarction and sudden cardiac death was performed. *Results*: Reports based on routinely collected data from population statistics ($n = 5$) generally reported a lower odds ratio (OR) of an event on Monday than studies with a confirmed diagnosis ($n = 16$). The pooled OR estimate based on population statistics was 1.04 (95%CI: 1.03; 1.05), whereas the pooled OR estimate based on confirmed diagnoses was 1.19 (95%CI: 1.17; 1.21). Subgroup analysis yielded an OR of 1.19 (95%CI: 1.07; 1.31) for men and 1.15 (95%CI: 0.99; 1.32) for women. Odds ratios for patients younger than 65 years of age and 65 or older were 1.22 (95%CI: 1.09; 1.36) and 1.16 (95%CI: 1.07; 1.27), respectively. The differences between subgroup odds ratios were not statistically significant. *Conclusion*: The incidence of sudden cardiac death is markedly increased on Monday, similar for men and women, and for subjects below and above 65 years of age.

Key words: Atherosclerosis, Cardiovascular disease, Circaseptan variation, Review, Sudden cardiac death

Introduction

Even though heart attacks and other cardiovascular events generally strike by surprise, their occurrence is by no means random. Over the past years we have repeatedly been warned to beware of Monday mornings in winter [1]. A range of studies has described cyclical patterns in cardiovascular mortality. Peaks have been identified between 6: 00 and 12: 00 [2], during winter months [3], and on Mondays [1, 4]. In a review of 30 reports on the circadian (i.e., within one day) pattern of cardiovascular events, Cohen et al. [2] estimated that 8.8% of all acute myocardial infarctions and 6.8% of sudden cardiac deaths are attributable to the morning excess of cardiovascular mortality. The magnitude of the excess incidence on Mondays, however, remains unknown.

The main pathophysiological mechanism has been proposed to be 'triggering' or disruption of a vulnerable atherosclerotic plaque [5]. Several possible triggers have been suggested, including natural rhythmic fluctuations in fibrinogen, cortisol, endothelial function and sympathetic stimulus [6]; but also rhythms in human activity like the work-leisure cycle, mental stress, physical activity [7], weekend binge drinking [8] and even watching an important football match [9].

To further explore the weekly pattern in cardiovascular mortality, we analysed the occurrence of sudden cardiac death in a meta-analysis of studies reporting on weekly variation in cardiovascular events. Since potential triggering factors may differ by gender and age subgroup analyses were performed.

Methods

Selection of publications

A PubMed Medline (www.ncbi.nlm.nih.gov) search of research papers in the English language, reporting weekly variation in cardiovascular events, published between January 1980 and September 2002 was performed. The bibliographies of the retrieved publications were reviewed and relevant citations were also evaluated. All papers retrieved with this strategy were entered in the 'Science citation expanded' database (ISI web of Science – www.isi.com) to retrieve more recent publications that refer to the former. In total, 27 papers were identified [4, 11–36]. These papers were reviewed and the main results were extracted separately by two of the authors (DW and MB). A summary is shown in Table 1.

Studies with relevant data were selected to obtain pooled estimates of the risk of a cardiovascular event on Monday. Criteria for inclusion in the pooled analysis were: definition of cases as 'sudden cardiac death' or 'myocardial infarction', and tables or

Table 1. Studies reporting on weekly variation in cardiovascular events

Ref	First author	Publication year	Country	Definition of cases	Source	Excess day
Angina Pectoris or sudden cardiac death						
[4]	Rabkin	1980	Canada	Sudden death or acute myocardial infarction	Manitoba study	Monday
[11]	Thompson	1992	UK	Acute myocardial infarction	Hospital records	Monday
[12]	Gnecchi-Ruscone	1994	Italy	Angina Pectoris	GISSI 2 study	Monday
[13]	Maron	1994	USA	Sudden death or cardiac arrest	Hospital records	None
[14]	Willich	1994	Germany	Acute myocardial infarction or Sudden death	MONICA study Augsburg	Monday
[15]	van der Palen	1995	New Zealand	Myocardial infarction or coronary death	Hospital records	None
[16]	Spielberg	1996	Germany	Acute myocardial infarction	Dessau myocardial infarction registry	Monday
[17]	Peters	1996	USA	Non fatal acute myocardial infarction	CAST study	Monday
[18]	Sayer	1997	UK	Acute myocardial infarction	Hospital records	None
[19]	Ku	1998	Taiwan	Acute myocardial infarction	Hospital records	Sunday low
[20]	•Zhou	1998	China	Acute myocardial infarction	Hospital records	Saturday
[22]	Bleyer	1999	USA	Sudden cardiac death	USRDS cohort	Monday
[22]	•Bleyer	1999	USA	Sudden cardiac death	CMAS cohort	Monday
[21]	•Peckova	1999	USA	Sudden cardiac death	Paramedic field report	Monday
[23]	Vehviläinen	1999	Finland	Angina Pectoris	Referral from primary to secondary care	Monday
[24]	Arntz	2000	Germany	Sudden death	Emergency patients	Monday
[37]	Witte	2004	Netherlands	Sudden cardiac death	Confirmed municipal death registry	Monday
Cardiac death in routine registers						
[25]	Massing	1985	Germany	ICD-9 code 410	Routine population statistics	Monday
[26]	Cornélissen	1993	Russia	Myocardial infarction	Routine registry of ambulance calls	None
[27]	Evans	2000	UK	ICD-9 codes 410-414	Routine population statistics	Monday
[28]	Marques-Vidal	2001	France	ICD-9 codes 410-414	Routine population statistics	None
[29]	Chenet	2001	Lithuania	ICD-9 codes 410-414	Routine population statistics	Monday
Other cardiovascular events						
[26]	Cornélissen	1993	Russia	Stroke	Routine registry of ambulance calls	Monday
[30]	Peters	1996	USA	Life-threatening ventricular arrhythmias	Patients with a implantable defibrillator	Monday
[31]	Vermeer	1997	Netherlands	Sub-arachnoidal haemorrhage	Hospital records	None
[32]	•Kuukasjärvi	2000	Finland	Acute leg ischaemia	Finnish vascular registry (FINNVASC)	Monday
[33]	Manfredini	2001	Italy	Ischaemic stroke	Hospital registry	Monday
[34]	Feigin	2001	Australia/New Zealand	Sub-arachnoidal haemorrhage	ACROSS and Auckland studies	None
[35]	Makie	2002	Japan	Cerebrovascular emergency	Emergency patients	Sunday low
[36]	Sumiyoshi	2002	Japan	Rupture of aneurysm of the abdominal aorta	Hospital records	None

figures presenting absolute mortality, incidence rates for each day of the week or the odds ratio and a 95% confidence interval for the occurrence of an event on Monday.

Nineteen papers were selected [4, 11–22, 24–29], reporting on 20 different populations. Five reports [25–29] based on routinely collected data from national or regional death registries were analysed separately from reports reporting confirmed diagnoses [4, 11–22, 24] (hospital records or data collected as part of a study), in order to deal with the considerable difference in numbers of patients, and misclassification of causes of death in routine registers. Data from our recent study in the city of Rotterdam [37] was included in the latter group. Pooled estimates were also obtained separately for men and women and for those aged under and over 65 years, based on a subset of studies which provided these data.

Data analysis

Absolute incidence data were abstracted from figures and tables of the selected studies. For each study, the odds of a cardiovascular event on Monday, compared to the other days of the week was calculated, with a 95% confidence interval. Pooled estimates for the odds ratio of a cardiovascular event on Monday compared to other days of the week were calculated according to the general variance based method [38]. Possible sources of heterogeneity such as differences in age and gender were analysed by calculating separate pooled estimates based on the studies that provided detailed data for these subcategories.

Results

Table 1 summarises the studies found by our search algorithm. For papers reporting results for different subgroups of patients [22] or for different case definitions [14], all relevant subgroups are shown separately. Age categories are not shown separately. The majority of the papers reported a higher incidence of sudden cardiac death or myocardial infarction on Monday. This appeared not to be the case for the miscellaneous group of 'other events', where a Monday peak is only reported for the occurrence of ventricular arrhythmias [30] and ischemic stroke [36].

Reports based on routinely collected data from population statistics, generally reported a lower OR of an event on Monday, than studies with a confirmed diagnosis (Figure 1). The pooled OR estimate based on population statistics was 1.04 (95%CI: 1.03; 1.05), whereas the pooled OR estimate based on confirmed diagnoses was 1.19 (95%CI: 1.17; 1.21).

Three studies with confirmed diagnosis provided data for age and gender specific analyses [11,16, 37]. Pooled subgroup analysis yielded an OR of 1.19 (95%CI: 1.07; 1.31) for men and 1.15 (95%CI: 0.99; 1.32) for women. Odds ratios for patients younger than 65 and 65 or older, were 1.22 (95%CI: 1.09; 1.36) and 1.16 (95%CI: 1.07; 1.27) respectively. The differences between pooled subgroup odds ratios were not statistically significant.

Discussion

The incidence of sudden cardiac death is markedly increased on Monday. This increase is similar for

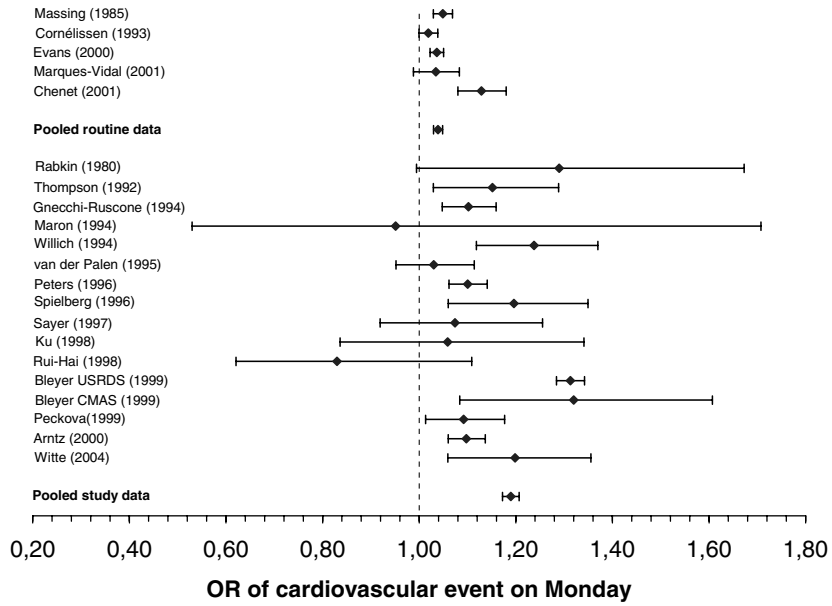

Figure 1. Odds Ratios (OR) for a myocardial infarction or sudden cardiac death on Monday, per study, and in two pooled estimates, for routinely collected data and for data collected within a study or confirmed registry.

men and women, and for subjects below and above 65 years of age.

A limitation in our meta-analysis is the small number of studies reporting on subgroups of patients by gender or age. The pooled subgroup analyses presented in this paper therefore, have less precision than the overall pooled analysis and fail to reach statistical significance.

Information on mechanisms underlying the rhythm in occurrence of cardiovascular events comes from studies in which the rhythm was attenuated or absent. For example, the identification of platelet aggregation as a mechanism behind the circadian pattern in myocardial infarction in the Physicians Health Study [38] came from finding a clear circadian pattern in the placebo group, but not in the aspirin group. Similar data exists for an attenuation of the circadian pattern in patients using β-blockers [18, 39, 40], and for a more pronounced circadian rhythm in the elderly [41–43] compared to younger people. The underlying mechanisms can be summarised as naturally occurring rhythmic fluctuations in human physiology, and socially determined rhythms in human behaviour. Both however, are generally thought to lead to a common final step resulting in the cardiovascular event; the disruption of a vulnerable atherosclerotic plaque [44]. Triggers, either physical or mental, internal or external, produce acute risk factors like vasoconstrictive, haemodynamic (arterial pressure) and haemostatic forces that, in turn, provoke disruption of the vulnerable plaque and lead to the formation of an occlusive thrombus [46]. In the case of weekly variation in incidence of cardiovascular events, triggers are most likely external, in the absence of weekly biological rhythms. Most of the reports reviewed in this paper, point to the mental stress of starting a new working week and the relative increase in activity as likely causes of the Monday peak. Apart from an explanation related to vulnerable plaque rupture, factors that initiate cardiac arrhythmia may also be important as explanation. Alcohol has been described as both underlying circadian and weekly variation curves as well as triggering cardiac arrhythmia [47–50].

Studies of routinely collected population data yielded a lower pooled estimate than studies with a confirmed diagnosis. This difference can probably be attributed to a higher degree of misclassification of causes of death in routine registry, leading to a dilution of the effect. The pooled odds ratio for the studies with a confirmed diagnosis therefore seems to be more accurate.

An additional possible source of heterogeneity is geographical location, or related differences in ethnicity. Two studies in a Chinese population did not find a peak on Monday, but rather a peak on Saturday [20], and a trough on Sunday [19]. Two Japanese studies, on cerebrovascular emergency [35] and rupture of an aneurysm of the abdominal aorta [36], found a Sunday low and no significant variation, respectively. The reason for the absence of a Monday peak in east-Asian populations remains elusive. Unfortunately, no evidence on weekly variation is available from populations adhering to different days of rest, e.g. an Islamic or Jewish calendar. Finally, nearly all studies reported a point estimate in favour of an increased risk on Monday, although not all studies were statistically significant. This may be due to the design of the studies (time window, definition of case, ascertainment of cases) and the size of the study (small, less precision).

An additional point of discussion is the practical consequence of the calculated number of excess deaths attributable to the Monday peak. Even though changes in weekly activity patterns or possibly medication might reduce peaks in mortality, it remains unclear whether these deaths are ultimately prevented, or if intervention will only result in a delay of the moment of death for a number of days. In the case of the attenuation of the morning peak by aspirin [40], the excess due to the morning peak has been shown to be avoidable. As stated by Ridker et al. [50], antiplatelet agents may exert at least part of their effect by altering the circadian variation of acute thrombosis, and by preventing the conversion of chronic atherosclerotic syndromes to acute disorders. In view of the common mechanism of triggering, it seems likely that these same concepts apply for the Monday peak. This has however currently not been explored.

In summary, this meta-analysis shows that there is a clear peak incidence of sudden cardiac death on Monday compared to the rest of the week which is similar for men and women and for subjects aged below or above 65 years of age.

References

1. Arntz HR, Muller-Nordhorn J, Willich SN. Cold Monday mornings prove dangerous: Epidemiology of sudden cardiac death. Curr Opin Crit Care 2001; 7: 139–144.
2. 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: 1512–1516.
3. Oberg AL, Ferguson JA, McIntyre LM, Horner RD. Incidence of stroke and season of the year: Evidence of an association. Am J Epidemiol 2000; 152: 558–564.
4. Rabkin SW, Mathewson FA, Tate RB. Chronobiology of cardiac sudden death in men. JAMA 1980; 244: 1357–1358.
5. Willich SN, Maclure M, Mittleman M, Arntz HR, Muller JE. Sudden cardiac death. Support for a role of triggering in causation. Circulation 1993; 87: 1442–1450.
6. Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: The lexicon of a new frontier. J Am Coll Cardiol 1994; 23: 809–813.

7. Tofler GH, Stone PH, Maclure M, et al. Analysis of possible triggers of acute myocardial infarction (the MILIS study). Am J Cardiol 1990; 66: 22–27.
8. Kauhanen J, Kaplan GA, Goldberg DE, Salonen JT. Beer binging and mortality: results from the Kuopio ischaemic heart disease risk factor study, a prospective population based study. BMJ 1997; 315: 846–851.
9. Witte DR, Bots ML, Hoes AW, Grobbee DE. Cardiovascular mortality in Dutch men during 1996 European football championship: Longitudinal population study. BMJ 2000; 321: 1552–1554.
10. Hoes AW, Grobbee DE, Lubsen J, Man in 't Veld AJ, van der DE, Hofman A. Diuretics, beta-blockers, and the risk for sudden cardiac death in hypertensive patients. Ann Intern Med 1995; 123: 481–487.
11. Thompson DR, Pohl JE, Sutton TW. Acute myocardial infarction and day of the week. Am J Cardiol 1992; 69: 266–267.
12. Gnecchi-Ruscone T, Piccaluga E, Guzzetti S, Contini M, Montano N, Nicolis E. Morning and Monday: Critical periods for the onset of acute myocardial infarction. The GISSI 2 Study experience. Eur Heart J 1994; 15: 882–887.
13. Maron BJ, Kogan J, Proschan MA, Hecht GM, Roberts WC. Circadian variability in the occurrence of sudden cardiac death in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 1994; 23: 1405–1409.
14. Willich SN, Lowel H, Lewis M, Hormann A, Arntz HR, Keil U. Weekly variation of acute myocardial infarction. Increased Monday risk in the working population. Circulation 1994; 90: 87–93.
15. van der PJ, Doggen CJ, Beaglehole R. Variation in the time and day of onset of myocardial infarction and sudden death. N Z Med J 1995; 108: 332–324.
16. Spielberg C, Falkenhahn D, Willich SN, Wegscheider K, Voller H. Circadian, day-of-week, and seasonal variability in myocardial infarction: Comparison between working and retired patients. Am Heart J 1996; 132: 579–585.
17. Peters RW, Brooks MM, Zoble RG, Liebson PR, Seals AA. Chronobiology of acute myocardial infarction: Cardiac arrhythmia suppression trial (CAST) experience. Am J Cardiol 1996; 78: 1198–1201.
18. Sayer JW, Wilkinson P, Ranjadayalan K, Ray S, Marchant B, Timmis AD. Attenuation or absence of circadian and seasonal rhythms of acute myocardial infarction. Heart 1997; 77: 325–329.
19. Ku CS, Yang CY, Lee WJ, Chiang HT, Liu CP, Lin SL. Absence of a seasonal variation in myocardial infarction onset in a region without temperature extremes. Cardiology 1998; 89: 277–282.
20. Zhou RH, Xi B, Gao HQ, et al. Circadian and septadian variation in the occurrence of acute myocardial infarction in a Chinese population. Jpn Circ J 1998; 62: 190–192.
21. Chenet L, Britton A. Weekend binge drinking may be linked to Monday peaks in cardiovascular deaths. BMJ 2001; 322: 998.
22. Bleyer AJ, Russell GB, Satko SG. Sudden and cardiac death rates in haemodialysis patients. Kidney Int 1999; 55: 1553–1559.
23. Vehvilainen AT, Kumpusalo EA, Takala JK. They call it stormy Monday – Reasons for referral from primary to secondary care according to the days of the week. Br J Gen Pract 1999; 49: 909–911.
24. Arntz HR, Willich SN, Schreiber C, Bruggemann T, Stern R, Schultheiss HP. Diurnal, weekly and seasonal variation of sudden death. Population-based analysis of 24,061 consecutive cases. Eur. Heart J 2000; 21: 315–320.
25. Massing W,.Angermeyer MC. Myocardial infarction on various days of the week. Psychol Med 1985; 15: 851–857.
26. Cornelissen G, Breus TK, Bingham C, et al. Beyond circadian chronorisk: Worldwide circaseptan-circasemiseptan patterns of myocardial infarctions, other vascular events, and emergencies. Chronobiologia 1993; 20: 87–115.
27. Evans C, Chalmers J, Capewell S, et al. "I don't like Mondays"-day of the week of coronary heart disease deaths in Scotland: Study of routinely collected data. BMJ 2000; 320: 218–219.
28. Marques-Vidal P, Arveiler D, Amouyel P, Ducimetiere P, Ferrieres J. Myocardial infarction rates are higher on weekends than on weekdays in middle aged French men. Heart 2001; 86: 341–342.
29. Chenet L, Britton A, Kalediene R, Petrauskiene J. Daily variations in deaths in Lithuania: The possible contribution of binge drinking. Int J Epidemiol 2001; 30: 743–748.
30. Peters RW, McQuillan S, Resnick SK, Gold MR. Increased Monday incidence of lifethreatening ventricular arrhythmias. Experience with a third-generation implantable defibrillator. Circulation 1996; 94: 1346–1349.
31. Vermeer SE, Rinkel GJ, Algra A. Circadian fluctuations in onset of subarachnoid hemorrhage. New data on aneurysmal and perimesencephalic hemorrhage and a systematic review. Stroke 1997; 28: 805–808.
32. Peckova M, Fahrenbruch CE, Cobb LA, Hallstrom AP. Weekly and seasonal variation in the incidence of cardiac arrests. Am Heart J 1999; 137: 512–515.
33. Manfredini R, Casetta I, Paolino E, et al. Monday preference in onset of ischemic stroke. Am J Med 2001; 111: 401–403.
34. Feigin VL, Anderson CS, Anderson NE, Broad JB, Pledger MJ, Bonita R. Is there a temporal pattern in the occurrence of subarachnoid hemorrhage in the southern hemisphere? Pooled data from 3 large, population-based incidence studies in Australia, 1981 to 1997. Stroke 2001; 32: 613–619.
35. Makie T, Harada M, Kinukawa N, et al. Association of meteorological and day-of-the-week factors with emergency hospital admissions in Fukuoka, Japan. Int J Biometeorol 2002; 46: 38–41.
36. Sumiyoshi M, Kojima S, Arima M, et al. Circadian, weekly, and seasonal variation at the onset of acute aortic dissection. Am J Cardiol 2002; 89: 619–623.
37. Witte DR, Grobbee DE, Bots ML, Hoes AW. Excess cardiac mortality on Monday: The importance of gender, age and hospitalisation. Eur J Epidemiol 2005;
38. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987; 9: 1–30.
39. Ridker PM, Manson JE, Buring JE, Muller JE, Hennekens CH. Circadian variation of acute myocardial infarction and the effect of low-dose aspirin in a randomized trial of physicians. Circulation 1990; 82: 897–902.

40. Willich SN, Linderer T, Wegscheider K, Leizorovicz A, Alamercery I, Schroder R. Increased morning incidence of myocardial infarction in the ISAM Study: Absence with prior beta-adrenergic blockade. ISAM Study Group. Circulation 1989; 80: 853–858.
41. Woods KL, Fletcher S, Jagger C. Modification of the circadian rhythm of onset of acute myocardial infarction by long-term antianginal treatment. Br Heart J 1992; 68: 458–461.
42. Yamasaki F, Seo H, Furuno T, et al. Effect of age on chronological variation of acute myocardial infarction onset: Study in Japan. Clin Exp Hypertens 2002; 24: 1–9.
43. Mitler MM, Hajdukovic RM, Shafor R, Hahn PM, Kripke DF. When people die. Cause of death versus time of death. Am J Med 1987; 82: 266–274.
44. Morning peak in the incidence of myocardial infarction: Experience in the ISIS-2 trial. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Eur Heart J 1992; 13: 594–598.
45. Servoss SJ, Januzzi JL, Muller JE. Triggers of acute coronary syndromes. Prog Cardiovasc Dis 2002; 44: 369–380.
46. Davies MJ. Stability and instability: two faces of coronary atherosclerosis. The Paul Dudley White Lecture 1995. Circulation 1996; 94: 2013–2020.
47. Wannamethee G, Shaper AG. Alcohol and sudden cardiac death. Br Heart J 1992; 68: 443–448.
48. Ryan JM, Howes LG. Relations between alcohol consumption, heart rate, and heart rate variability in men. Heart 2002; 88: 641–642.
49. Djousse L, Levy D, Benjamin EJ. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. Am J Cardiol 2004; 93: 710–713.
50. Ridker PM, Willich SN, Muller JE, Hennekens CH. Aspirin, platelet aggregation, and the circadian variation of acute thrombotic events. Chronobiol Int 1991; 8: 327–335.

Address for correspondence: Dr M.L. Bots, Julius Center for Health Sciences and Primary Care, Huispostnumer Str 6.131, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
Phone: +31-30-250-9352; Fax: +31-30-250-5485
E-mail: m.l.bots@jc.azu.nl