Circadian Variation in the Timing of Stroke Onset : A Meta-analysis

William J. Elliott

Stroke 1998, 29:992-996
doi: 10.1161/01.STR.29.5.992
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Circadian Variation in the Timing of Stroke Onset
A Meta-analysis

William J. Elliott, MD, PhD

Background and Purpose—Acute myocardial infarction and sudden death display a circadian rhythm, with a higher risk between 6 AM and noon. Some reports suggest that stroke does not follow such a circadian variation and that hemorrhagic stroke occurs more often during the evening.

Methods—A meta-analysis of 31 publications reporting the circadian timing of 11 816 strokes was performed, subdividing (when possible) by the type of stroke, according to the time of onset of symptoms. When precise timing was not given, strokes were distributed evenly (that is, biasing toward the null hypothesis of lack of circadian variation).

Results—All subtypes of strokes displayed a significant ($P<0.001$) circadian variation in time of onset, whether divided into 3-, 4-, or 6-hour time periods. There was a 49% increase (95% confidence interval, 44% to 55%) in stroke of all types between 6 AM and noon (compared with expectations if no circadian variation was present), which is a 79% (95% confidence interval, 72% to 87%) increase over the normalized risk of the other 18 hours of the day. There were 29% fewer strokes between midnight and 6 AM, a 35% decrease compared with the other 18 hours of the day. All three subtypes of stroke had a significantly higher risk between 6 AM and noon (55% for 8250 ischemic strokes; 34% for 1801 hemorrhagic strokes, and 50% for 405 transient ischemic attacks).

Conclusions—These data support the presence of a circadian pattern in the onset of stroke, with a significantly higher risk in the morning. **(*Stroke*. 1998;29:992-996.)**

Key Words: circadian variation ■ meta-analysis ■ stroke onset

Several types of cardiovascular events, including acute myocardial infarction and sudden cardiac death, display significant circadian variation in the timing of onset of symptoms. A recent meta-analysis of the 30 reports from across the world, which included 66 635 acute myocardial infarctions, has demonstrated a 40% excess risk between 6 AM and noon compared with the rest of the day.[1] A similar meta-analysis of 19 studies involving 19 390 sudden cardiac deaths indicated a 29% increase in risk for this 6 AM to noon time period.[1] Some believe this morning excess of cardiovascular risk parallels the usual circadian pattern of physical activity, blood pressure, plasma catecholamines, and/or plasma cortisol.[2–5]

Early studies of the timing of acute stroke, however, indicated that many afflicted patients reported awakening with new neurologic deficits, and several reports indicated that acute strokes tended to occur either during the evening hours or during sleep.[6–8] This led to the conclusion that especially because acute therapies for stroke-in-evolution were not particularly effective, there was little reason to consider acute stroke as a medical emergency because the onset of symptoms was thought to occur during sleep, when most patients would not recognize them.

More recently, data have been reported from many different countries regarding both timing of the onset of acute stroke and the subtype of stroke. A systematic review of these data was therefore undertaken to consider whether there was a period during the 24 hours of the day when stroke onset was more likely, to estimate the level of excess risk, and to determine whether this period of increased risk was different for various subtypes of stroke (ischemic, hemorrhagic, or transient ischemic attack).

Subjects and Methods

A MEDLINE search of publications in all languages from 1966 to December 1997 was performed with both text word searching and the appropriate MESH headings of "circadian variation," and "stroke, cerebrovascular accident, transient ischemic attack, or brain attack." The bibliographies of each of the retrieved publications that contained primary data about the timing of the onset of stroke were reviewed, and relevant citations in these listings were also evaluated for inclusion in the meta-analysis. Reported data about timing of stroke, the hourly time periods involved, and the subtype of stroke were abstracted and entered into a computerized spreadsheet/database.[9] When the same population was reported more than once,[10–12] only the most descriptive report was included. Instead of reporting the hourly incidence of stroke onset, several publications instead provided data only in the form of mathematical models (for example, cosinor analysis)[13–15]; this necessitated estimating hourly stroke onset rates from the parameters given in the reports, according to standard procedures.[14–16] Some reports[17] also presented the primary data as figures, in which case, estimates of hourly stroke onset were derived

Received January 26, 1998; final revision received March 6, 1998; accepted March 6, 1998.

From the Department of Preventive Medicine, Rush Medical College of Rush University, and Rush–Presbyterian–St Luke's Medical Center, Chicago, Ill.

Presented in part at the 12th Annual Meeting of the American Society of Hypertension, San Francisco, Calif, May 30, 1997.

Correspondence to William J. Elliott, MD, PhD, Department of Preventive Medicine, Rush–Presbyterian–St Luke's Medical Center, 1725 West Harrison St, Suite 117, Chicago, IL 60612.

from photocopied enlargements of the published figures and appropriate interpolation. When reports identified the onset of stroke symptoms during sleep, data that distributed the risk across the known hours of sleep were retained in the meta-analysis. Within each report, data from patients whose stroke onset times were unknown (and could not be identified as occurring during sleep) were excluded from the meta-analysis (when it was possible to distinguish them in the original publication), because reports about strokes without times of onset were also excluded from the meta-analysis.

Because most publications did not report an hourly breakdown of the onset of acute stroke but instead 2- to 20-hour time blocks, it was necessary to divide the 24-hour day into standardized blocks of time, and reallocate the observed numbers of strokes accordingly. When precise timing was not given, or when the original report did not include data from each of the 24 hourly divisions, the number of strokes were distributed evenly throughout the appropriate hours. This technique systematically biases the meta-analysis toward the null hypothesis of a lack of circadian variation. In addition, a "worst-case scenario" was considered, for which all of the "untimed" strokes cited in the original reports were arbitrarily assigned to the time period having the fewest observed strokes.

Statistical testing for the meta-analysis was performed with traditional methodology for homogeneity and significance; χ^2 techniques (for goodness of fit to the null model of equal distribution of strokes) were used, along with 95% confidence intervals, to evaluate the circadian pattern of stroke onset.[18] Two strategies were used to estimate the relative risk of strokes occurring at specific time periods: One assumed that all strokes would be evenly distributed in onset among the 24 hours of the day, and therefore compared the observed proportion relative to the proportion expected, based on the total number reported. The second method is based on a comparison of the observed number of strokes compared with the average for the other hours of the day, normalized for hours under consideration.[1] In this analysis, the expected number of events that were reported to have occurred, for instance, between 6 AM and noon, were compared with the number of events occurring in the remaining 18 hours of the day (divided by 3, to normalize for the number of hours in the time period under consideration), and the relative risk was the number of strokes actually reported, divided by the number expected.

Results

Thirty-one publications[6–8,13–15,17,19–21,26–45] were retrieved that contained primary data regarding strokes with known times of onset; these included 11 816 patients and are summarized in the Table. Despite some rather large differences across studies in reported sample size (59 to 1075), outcomes (fatal versus nonfatal), and types of stroke studied (ischemic versus hemorrhagic versus other), most of the studies showed a similar diurnal pattern of stroke incidence. When all strokes are categorized according to the midnight to 6 AM to noon to 6 PM divisions of the day, as in Cohen et al,[1] a "morning excess" of all stroke is seen between 6 AM to noon (Figure 1, bars A), which corresponds to a 49% increased relative risk (95% confidence interval [CI]: 44% to 55%) compared with the number expected if there had been no circadian variation in stroke onset ($\chi^2=1133$, 3 *df*, $P<0.001$), or a 79% increased relative risk (95% CI, 72% to 87%) compared with the normalized rate for the remaining 18 hours of the day. The 6-hour time period with the lowest risk for all stroke is between midnight and 6 AM, which has a 29% (95% CI, 25% to 32%) lower relative risk (compared with expected number of strokes had there been no circadian variation) or 35% (95% CI, 32% to 38%) lower relative risk than expected if compared with the other 18 hours of the day.

Across all original reports, there were 1222 strokes for which the time of onset was unrecorded or uncertain. If one places all these "untimed" strokes in the time period of lowest risk (a "worst-case scenario"), there is still a significant circadian variation in the risk of stroke ($\chi^2=725$, 3 *df*, $P<0.001$). The 6 AM to noon time period then has a 35% (95% CI, 30% to 41%) increased risk compared with the expected number of strokes had there been no circadian variation, or 54% (95% CI, 48% to 60%) increased risk if compared with the normalized rate for the other 18 hours of the day.

It is also possible to rearrange the strokes for which the time of onset was reported into other periods of interest, slicing the 24 hours of the day into different time blocks. The most analogous to the primary result given above is the 3 AM to 9 AM to 3 PM to 9 PM quarters of the day. Allocating the strokes reported into these time periods results in a 17% (95% CI, 12% to 22%) increase in relative risk for all stroke between 3:01 and 9 AM and a 23% (95% CI, 18% to 29%) increase in risk between 9:01 and 3 PM (compared with numbers expected if there had been no circadian variation in stroke onset ($\chi^2=599$, 3 *df*, $P<0.001$). If the normalized rate for the remaining 18 hours of the day is used as the comparator, there is a 24% (95% CI, 19% to 30%) increased relative risk between 3:01 and 9 AM and a 34% (95% CI, 28% to 40%) increased relative risk of stroke in the next 6-hour period. The time period between 9:01 PM and 3 AM has the lowest number of strokes (33% [95% CI, 30% to 37%] reduced relative risk compared with expectations if there had been no circadian variation and 40% [95% CI, 38% to 43%] reduced relative risk compared with the other 18 hours of the day).

If one reanalyzes the reported strokes according to their time of onset during six 4-hour periods of the day, a highly significant circadian variation is seen in the meta-analysis ($\chi^2=879$, 5 *df*, $P<0.001$). The highest risk is found between 8:01 AM and noon (a 45% [95% CI, 38% to 52%] increase compared with what would have been expected if there were no circadian variation in stroke onset and a 59% [95% CI, 51% to 68%] increase compared with the normalized rate for the remaining 20 hours of the day); the lowest is found between midnight and 4 AM (35% [95% CI, 31% to 40%] or 40% [95% CI, 35% to 45%] reduced relative risk, respectively). Finally, if the reported strokes are redistributed according to their times of onset during the eight 3-hour periods of the day, there is still a significant result in the meta-analysis, rejecting the null hypothesis of no circadian variation in time of stroke onset ($\chi^2=1202$, 7 *df*, $P<0.001$). The time period of highest risk is found between 6:01 and 9 AM (58% [95% CI, 48% to 67%] increase compared with the expected value if all strokes had been evenly distributed and a 72% [95% CI, 62% to 83%] increase compared with the value expected for the other 21 hours in the day), with the time between 9:01 and noon following close behind (42% and 51% [95% CI, 41% to 61%] increase in relative risk, respectively). The time period with the lowest number of events is from midnight to 3 AM (36% [95% CI, 31 to 40%] and 44% [95% CI, 40% to 48%] decrease in relative risk, respectively).

Strokes of All Types, Divided into 6-Hour Time Blocks, Beginning at Midnight

Author	Type of Stroke	Time Blocks (h), starting at	n	00:00–05:59	06:00–11:59	12:00–17:59	18:00–23:59	Untimed
Vermeer et al[21]	Subarachnoid hemorrhage	2, MN	258	31	72	84	71	27
Hayashi et al[19]	Fatal stroke	2, MN	529	93	141	120	175	15
Haapaniemi et al[26]	Ischemic stroke	6, 2 AM	610	170	189	149	102	113
Kelly-Hayes et al[27]	Any stroke	4, MN	401	71	180	100	50	234
Roberts et al[28]	Any stroke	1, MN	68	10	33	14	11	6
Pardiwalla et al[29]	Any stroke	8, 6 AM	182	26	82	46	28	0
Gallerani et al[15]	Any stroke	6, MN	897	107	330	276	184	80
Haapaniemi et al[30]	First ischemic stroke	2, MN	609	101	277	131	100	0
Wroe et al[31]	Any first stroke	2, MN	554	59	265	137	93	80
Franke et al[32]	IC hemorrhage	6, MN	138	21	37	52	28	19
Ricci et al[33]	Any stroke	3, MN	368	32	180	105	51	7
Ince[34]	Infarction	6, MN	110	14	38	42	16	0
Sloan et al[35]	IC and SA hemorrhage	2, MN	375	32	134	124	85	105
Toni et al[36]	Ischemic stroke	1, MN	80	1	36	18	25	0
Lu[37]	Ischemic stroke	2, MN	1032	223	361	224	224	0
Herderscheê et al[38]	Any stroke	6, MN	85	13	31	27	14	35
Arboix et al[39]	Any stroke	6, MN	204	52	72	51	29	2
Manfredini et al[14]	Any stroke	1?*, MN?	108	16	22	38	32	33
Argentino et al[40]	Ischemic stroke	1, MN	426	66	239	86	35	0
Johansson et al[13]	Any stroke	1?*, MN?	400	67	145	134	54	97
Marsh et al[41]	Ischemic stroke	2, MN	151	20	86	21	24	0
Pasqualetti et al[20]	Any stroke	1, MN	667	193	183	151	140	65
Marler et al[42]	Ischemic stroke	2, MN	1075	85	485	320	185	106
Van der Windt et al[43]	Cerebral infarction	1, MN	59	5	22	24	8	7
Tsementzis et al[17]	Any stroke	2, MN	543	83	183	138	139	14
Kaps[44]	Ischemic stroke	12, 7 AM	545	94	200	179	72	0
Jovocic[45]	Any stroke?	1, MN	85	7	43	16	19	0
Hossmann and Zülch[8]	Any stroke	2–6, 1 AM	707	254	179	122	152	141
Marshall[7]	Any stroke	6, MN	256	81	69	59	47	0
Agnoli et al[6]	Any stroke?	8, 6 AM	167	14	69	31	53	36
Olivares et al[46]	Any stroke	6, MN	127	53	32	16	26	0
Totals			11 816	2094	4415	3035	2272	1222

MN indicates midnight; IC, intracranial; SA, subarachnoid.
*Denotes mathematical model.

Because there are some reports from Japan,[19] especially regarding hemorrhagic stroke,[20,21] which suggest that there may be differences in circadian variation of stroke timing according to the subtype of stroke of interest, meta-analyses of ischemic and hemorrhagic stroke (including subarachnoid and intracerebral bleeds), and transient ischemic attack were also carried out. The results (when distributed into the 6-hour time periods beginning immediately after midnight) are shown in Figure 1. These data suggest that for each subtype of stroke studied, there is an increase in risk during the early morning hours. There were 21 studies (including 8250 patients) of ischemic stroke, which was 55% (95% CI, 48% to 62%) more likely between 6 AM and noon. The 13 studies of 1801 patients with hemorrhagic stroke also showed a significant circadian variation (Figure 1B); the risk was 34% (95% CI, 21% to 49%) greater between 6 AM and noon. The "morning excess" is even statistically significant for transient ischemic attack (TIA), in which only two studies form the basis for a meta-analysis of 405 patients, but a χ^2 value of 95 (3 *df*, $P<0.001$) is obtained, indicating a 50% (95% CI, 20% to 85%) increased risk of TIA between 6:01 AM and noon and an even more impressive 76% (95% CI, 64% to 84%) decreased risk of TIA between midnight and 6 AM (all compared with the random distribution of TIAs across the 24 hours of the day). The pertinent percentages for these time periods (with the 18 remaining hours of the day as comparator) are an 80% (95% CI, 43% to 126%) increase, or an 81% (95% CI, 72% to 87%) decrease, in risk for 6 AM to noon or midnight to 6 AM, respectively. A statistically significant circadian pattern of timing of stroke onset was seen for all subtypes of strokes, even when the 24 hours of the day were divided into 4-hour (Figure 2) or 3-hour periods (data not shown).

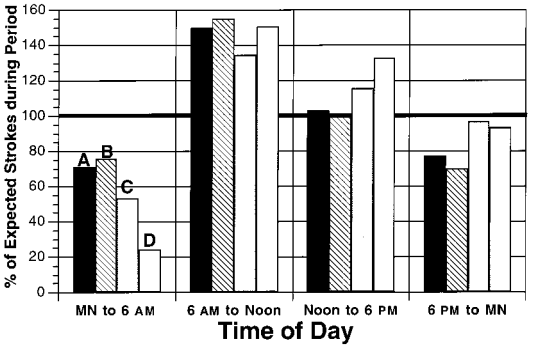

Figure 1. Circadian patterns of onset of symptoms of stroke, subdivided by subtype of stroke, according to four 6-hour time periods. Dark bars (A) show the distribution of all types of stroke (n=11 816); diagonally-striped bars (B) correspond to ischemic stroke (n=8250); gray bars (C) represent hemorrhagic stroke (n=1801); and light bars (D) show the data for transient ischemic attacks (n=405).

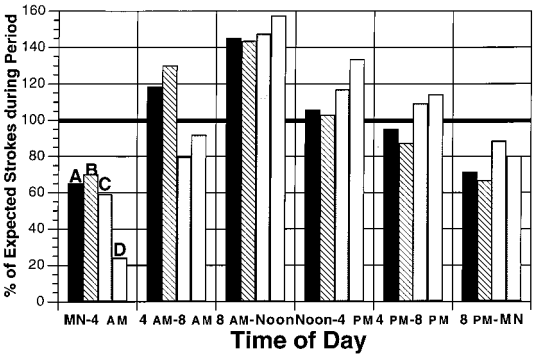

Figure 2. Circadian patterns of onset of symptoms of stroke, subdivided by subtype of stroke, according to six 4-hour time periods. Dark bars (A) show the distribution of all types of stroke (n=11 816); diagonally-striped bars (B) correspond to ischemic stroke (n=8250); gray bars (C) represent hemorrhagic stroke (n=1801); and light bars (D) show the data for transient ischemic attacks (n=405).

Discussion

These data from a meta-analysis of the world's 31 published studies on the circadian timing of stroke onset indicate that like acute myocardial infarction and sudden cardiac death, there is an increased risk of the onset of acute stroke during the early morning hours. The data are remarkably consistent across the various subtypes of stroke, and indicate, for ischemic stroke, hemorrhagic stroke, and even transient ischemic attacks, that the excess risk during the 6 AM to noon time period is significantly higher than would be expected by chance: 89%, 52%, and 80% (95% CI, 89% to 99%, 36% to 69%, and 43% to 126%, respectively, compared with the normalized risk for the other 18 hours of the day). Similarly, there is a significantly lower risk of stroke during the nighttime hours (midnight to 6 AM) for each stroke subtype: 30%, 54%, and 81% (95% CI, 26% to 33%, 48% to 60%, 72% to 87%, respectively, compared with the normalized risk for the other 18 hours of the day). Even when all the strokes in the original publications for which a time of onset could not be accurately determined are incorporated into the meta-analyses in a "worst-case scenario" in each division of the hours of the day, there is a significant circadian variation in the timing of stroke onset.

As with the results of all meta-analyses,[22] these conclusions should be interpreted cautiously. The reports that provide the raw data for the meta-analysis were seldom population based, may have been subject to "publication bias," and typically rely on recall of information from patients or witnesses as to what time the stroke symptoms actually began. The raw data are not "wake-time adjusted" and do not identify strokes occurring among individuals who work night or evening shifts, who have a higher blood pressure on arising but not in the typical 6 to 8 AM time frame. There are few reports that divide the numbers of strokes according to each of the 24 hours of the day, and it is possible that the categorization of stroke frequencies into the arbitrary time periods for the meta-analysis is incorrect. It would be expected, however, that any such inaccuracies would bias the results toward the null hypothesis, because distributing the number of strokes evenly throughout the period reported should increase the chances that no significant circadian variation in stroke frequency would be noted. Last, the results of the smaller time periods (3- or 4-hour "slices") may underestimate the true circadian variation in stroke onset because statistical power of the meta-analysis diminishes as the number of time periods increases.

The finding that the early morning hours (and not the nighttime hours) have the highest risk of the onset of stroke symptoms has two broad implications. The first is that patients should no longer be told that stroke symptoms are not a medical emergency. Although this may have been sound public policy when acute treatments for stroke were not available, there is now some evidence that acute emergent treatments for cerebral ischemia can be delivered in a timely fashion and result in improved long-term outcomes.[23,24] The results of this meta-analysis contradict older conclusions that "strokes are more likely to occur during sleep."[19] This meta-analysis indicates that irrespective of the type of stroke, most patients will be awake when the onset of stroke symptoms occurs. The recognition of new neurologic deficits should prompt afflicted patients and their families to consider these as a medical emergency (or "brain attack"). The second implication of these conclusions has to do with some modalities useful in stroke prevention. Blood pressure is often considered one of the most powerful risk factors for stroke and has a circadian variation that essentially parallels the circadian variation in stroke onset. Antihypertensive agents administered in the morning ought to have a long duration of action to still have an effect on the early morning rise in blood pressure. It is tempting to speculate that antihypertensive agents that specifically target the early morning rise in blood pressure and heart rate, without reducing blood pressure severely during the night, might be more advantageous in controlling the 20% rise in blood pressure during the hours around awakening. This appears also to be the time of day associated with an increased risk of stroke, myocardial infarction, and sudden cardiac death. At least one long-term clinical trial is currently enrolling patients to examine this question.[25]

This meta-analysis of 11 816 strokes provides strong evidence that the onset of stroke symptoms has a circadian variation, with a higher risk in the early morning hours (6 AM to noon), and lower risk during the nighttime period (midnight to 6 AM). Approximately 1 of every 8 strokes (1 of 7 ischemic strokes, 1 of 10 hemorrhagic strokes, and 1 of 8 transient ischemic attacks) is attributable to the morning excess.

References

1. 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;79:1512–1515.
2. Muller JE, Mangel B. Circadian variation and triggers of cardiovascular disease. *Cardiology*. 1994;85(suppl 2):3–10.
3. Cooke HM, Lynch A. Biorhythms and chronotherapy in cardiovascular disease. *Am J Hosp Pharm*. 1994;51:2569–2580.
4. Smolensky MH, D'Alonzo GE. Medical chronobiology: concepts and applications. *Am Rev Respir Dis*. 1995;147:S2–S19.
5. Straka RJ, Benson SR. Chronopharmacologic considerations when treating the patient with hypertension: a review. *J Clin Pharmacol*. 1996;36:771–782.
6. Agnoli A, Manfredi M, Mossuto L, Piccinelli A. Rapport entre les rythmes héméronyctaux de la tension artérielle et sa pathogénie de l'insuffisance vasculaire cérébrale. *Rev Neurol (Paris)*. 1975;131: 597–606.
7. Marshall J. Diurnal variation in occurrence of strokes. *Stroke*. 1977;8: 230–231.
8. Hossmann V, Zülch KJ. *Circadian Variations of Hemodynamics and Stroke*. Berlin/New York: Springer-Verlag; 1979:171–180.
9. Lau J, Ioannidis JPA, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;127:820–826.
10. Lu JQ, Han ZY, Zhu YH, Zhang Y, Yan ZL, Li W. Quexuexing naoxueguanbing fabing suijian de zhouye chayi [in Chinese]. *Zhonghua Yixue Zazhi (National Medical Journal of China)*. 1991;71:176.
11. Hossmann V. Circadian changes of blood pressure and stroke. In: Zulch KJ, ed. *Cerebral Circulation and Stroke*. Berlin/Heidelberg/New York: Springer; 1971:203–208.
12. Arboix A, Marti-Vilalta JL. Ritmo nictemeral y patologia vascular cerebral: Estudio clinico prospectivo de 206 casos. *Med Clin (Barc)*. 1988;90:358–361.
13. Johansson BB, Norrving B, Widner K, Wu J, Halberg F. Stroke incidence: circadian and circaseptan (about weekly) variations in onset. *Prog Clin Biol Res*. 1990;341A:427–436.
14. Manfredini R, Squarzoni G, Gallerani M, Franceschini F, Bariani L, Fersini C. Temporal organization of cerebrovascular accidents: a retrospective, preliminary study about stroke in Ferrar, Italy. *Eur Rev Med Pharmacol Sci*. 1990;12:223–228.
15. Gallerani M, Manfredini R, Ricci L, Cocurullo A, Goldoni C, Bigoni, M, Fersini C. Chronobiological aspects of acute cerebrovascular diseases. *Acta Neurol Scand*. 1993;87:482–487.
16. Nelson W, Tong YL, Lee JK, Halberg F. Methods for cosinor-rhythmometry. *Chronobiologia*. 1979;6:305–323.
17. Tsementzis SA, Gill JS, Hitchcock ER, Gill SK, Beevers DG. Diurnal variation of and activity during the onset of stroke. *Neurosurg*. 1985;17: 901–904.
18. Der-Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
19. Hayashi S, Toyoshima H, Tanabe N, Miyanishi K. Daily peaks in the incidence of sudden cardiac death and fatal stroke in Niigata Prefecture. *Jpn Circ J*. 1996;60:193–200.
20. Pasqualetti P, Natali G, Casale R, Colantonio D. Epidemiological chronorisk of stroke. *Acta Neurol Scand*. 1990;81:71–74.
21. Vermeer SE, Rinkel GJE, 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.
22. LeLorier J, Grégoire G, Benhaddad A, Lapierre L, Derderian F. Discrepancies between meta-analyses and subsequent large randomized controlled trials. *N Engl J Med*. 1997;337:536–542.
23. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
24. Candelise L, Roncaglioni C, Aritzu E, Ciccone A, Maggioni AP. Thrombolytic therapy. From myocardial to cerebral infarction: the MAST-I Group: Multicentre Acute Stroke Trial. *Ital J Neurol Sci*. 1996;17:5–21.
25. Black HR, Elliott WJ, Neaton JD, Grandits G, Grambsch P, Grimm RH Jr, Hansson L, Lacoucière Y, Muller J, Sleight P, Weber MA, White WB, Williams G, Wittes J, Zanchetti A, Fakouhi TD, for the CONVINCE Research Group. Rationale and Design for the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) Trial. *Control Clin Trials*. In press.
26. Haapaniemi H, Hillbom M, Juvela S. Weekend and holiday increase in the onset of ischemic stroke in young women. *Stroke*. 1996;27: 1023–1027.
27. Kelly-Hayes M, Wolf PA, Kase CS, Brand FN, McGuirk JM, D'Agostino RB. Temporal patterns of stroke onset: the Framingham Study. *Stroke*. 1995;26:1343–1347.
28. Roberts MA, Oparo-Sem OK, Achaumpong JW. The diurnal variation of stroke in Ghana. *Trop Doct*. 1994;24:155–157.
29. Pardiwalla FK, Yeolekar ME, Bakshi SK. Circadian rhythm in acute stroke. *J Assoc Physicians India*. 1993;41:203–204.
30. Haapaniemi H, Hillbom M, Numminen H, Juvela S, Palomaki H, Kaste M. Early-morning increase in the onset of ischemic stroke. *Cerebrovasc Dis*. 1992;2:282–286.
31. Wroe SJ, Sandercock P, Bamford J, Dennis M, Slattery J, Warlow C. Diurnal variation in incidence of stroke: Oxfordshire community stroke project. *BMJ*. 1992;304:155–157.
32. Franke CL, van Swieten JC, van Gign J. Circadian and seasonal variation in the incidence of intracerebral hemorrhage. *Cerebrovasc Dis*. 1992;2: 44–46.
33. Ricci S, Celani MG, Vitali R, La Rosa F, Righetti E, Duca E. Diurnal and seasonal variations in the occurrence of stroke: a community-based study. *Neuroepidemiology*. 1992;11:59–64.
34. Ince B. Circadian variation in stroke [letter]. *Arch Neurol*. 1992;49:900.
35. Sloan MA, Price TR, Foulkes MA, Marler JR, Mohr JP, Heir DB, Wolf PA, Caplan LR. Circadian rhythmicity of stroke onset: intracerebral and subarachnoid hemorrhage. *Stroke*. 1992;23:1420–1426.
36. Toni D, Argentino C, Gentile M, Sacchetti ML, Girmenia F, Millefiorini E, Fieschi C. Circadian variation in the onset of acute cerebral ischemia: etiopathogenetic correlates in 80 patients given angiography. *Chronobiol Int*. 1991;8:321–326.
37. Lu J-Q. Traditional Chinese medical theory and human circadian rhythm in the occurrence of ischemic stroke [letter]. *Stroke*. 1991;22:1827.
38. Herderscheê D, Limburg M, Hijdra A, Bollen A, Pluvier J, te Water W. Timing of hospital admission in a prospective series of stroke patients. *Cerebrovasc Dis*. 1991;1:165–167.
39. Arboix A, Marti-Vilalta JL. Acute stroke and circadian rhythm [letter]. *Stroke*. 1990;21:826.
40. Argentino C, Toni D, Rasura M, Violi F, Sacchetti ML, Allegretta A, Balsano F, Fieschi C. Circadian variation in the frequency of ischemic stroke. *Stroke*. 1990;21:387–389.
41. Marsh EE III, Biller J, Adams HP Jr, Marler JR, Hulbert JR, Love RR, Gordon DL. Circadian variation in onset of acute ischemic stroke. *Arch Neurol*. 1990;47:1178–1180.
42. Marler JR, Price TR, Clark GL, Muller JE, Robertson T, Mohr JP, Hier DB, Wolf PA, Caplan LR, Foulkes MA. Morning increase in onset of ischemic stroke. *Stroke*. 1989;20:473–476.
43. Van der Windt C, Van Gijn J. Cerebral infarction does not occur typically at night. *J Neurol Neurosurg Psychiatry*. 1988;51:109–111.
44. Kaps M, Busse O, Hofmann O. Zur circadianen Häufigkeitsverteilung ischämischer Insulte. *Nervenarzt*. 1983;54:655–657.
45. Jovicic A. Bioritam i ishemiçni cerebrovaskularni poremeçaji. *Vojnosanit Pregl*. 1983;40:347–351.
46. Olivares L, Castaneda E, Grife A, Alter M. Risk factors in stroke: a clinical study in Mexican patients. *Stroke*. 1973;4:773–780.