Letters to the Editor

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Diurnal Variation in Stroke Onset in Atrial Fibrillation

To the Editor:

We read with interest the article by Engström et al. on cardiac arrhythmias and stroke and agree that apart from atrial fibrillation (AF), little scientific attention has been given to the associations between cardiac arrhythmias and stroke onset. Even in AF, we still need to know much more on the relation to stroke onset, as this arrhythmia is usually present in about 15% to 20% of patients with acute stroke and is associated with a 1.5- to 3.0-fold higher mortality than that for stroke patients who are in sinus rhythm. Strokes attributed to AF also tend to be more severe, with greater disability, longer hospital stay, and lower rate of patient discharge to own home.3,4

A diurnal variation in the onset of cardiac events and stroke is well recognized. Although the diurnal variation of stroke onset has generally been established in patients who are in sinus rhythm, we are unaware of any published data on diurnal variation of stroke onset in patients with AF. To investigate this further, we assessed the time of the stroke onset in 60 patients (21 men, mean ± SD age 76 ± 10 years) with first-onset stroke who were in AF on admission to our city center teaching hospital to determine the existence of any diurnal variation. Furthermore, antithrombotic therapy prescribed before admission and after discharge was noted.

There was a circadian rhythm of stroke onset among patients with atrial fibrillation, with a significantly higher number of strokes occurring between 6 AM and 6 PM and the least number of strokes occurring between midnight and 6 AM ($\chi^2$ test, $P = 0.025$; Figure, Table). CT scan reports were available for 37 patients (62%): 34 reported acute cerebral infarcts while 3 were reported to be normal. Two of the 34 cerebral infarcts showed areas of hemorrhagic transformation. None of the available CT scans reported primary hemorrhagic infarcts. Only 44% were taking antithrombotic therapy on admission: 8 were taking warfarin (13%), 16 aspirin (27%) and 2 both aspirin and warfarin (3%). Six patients died in hospital and 54 patients were discharged alive. On discharge, only 19 were taking warfarin (35%), 24 aspirin (44%) and 3 both aspirin and warfarin (6%).

Most of the reports on circadian variations suggest a peak in the incidence of events between 6 AM and noon. For example, most strokes occurred between 6 AM and noon,5 with the pattern being observed for both ischemic and hemorrhagic stroke as well as stroke subgroups.5-7 A recent meta-analysis8 reported a 49% increase in stroke of all types between 6 AM and noon, which was a 79% increase over the normalized risk of the other 18 hours of the day; however, there were 29% fewer strokes between midnight and 6 AM, a 35% decrease compared with the other 18 hours of the day. Thus, a significant clustering of stroke was observed between 6 AM and noon, although these data are mostly based on patients in sinus rhythm.

Though AF is an independent risk factor for stroke, we are not aware of any studies examining the circadian variation of stroke onset among patients with AF per se. Moreover, there appears to be lack of diurnal variation of hemostatic factors or platelet activation among patients with chronic AF, representing a persistently prothrombotic state associated with this arrhythmia.9

In conclusion, this pilot study demonstrates the existence of a circadian variation in stroke onset among patients with AF, with most strokes between 6 AM and 6 PM. Despite the evidence from randomized trials,10 antithrombotic therapy use in this high-risk group still remains suboptimal.

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<table>
<thead>
<tr>
<th>Time of Onset</th>
<th>Observed Number</th>
<th>Expected Number</th>
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<tbody>
<tr>
<td>6 AM–6 PM</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>6 PM–6 AM</td>
<td>18</td>
<td>30</td>
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Total $\chi^2=5.0$, $df=1$, $P = 0.025$.

References

Systemic Complement Activation in Ischemic Stroke

To the Editor:

Activation of the complement system has been reported in a variety of inflammatory diseases and neurodegenerative processes of the central nervous system, and recent evidence indicates that complement proteins and receptors are synthesized on or by glial cells and, surprisingly, neurons.1

In their study, Xi and colleagues2 furnish new indirect data on the activation of complement system after intracerebral hemorrhage (ICH) in rats and suggest a possible pharmacological manipulation preventing complement activation to reduce the brain edema in ICH. However, despite the large number of therapeutic interventions that decrease damage in experimental animals, many negative results have been produced in the history of therapy in cerebrovascular disease when the same agent is tested in clinical trials. Experimental studies are conducted on healthy, young animals under rigorously controlled laboratory conditions. However, the typical stroke patient is elderly with numerous risk factors and complicating disease (for example, diabetes, arterial hypertension, and heart disease). Therefore, we must have more strong data on complement activation in stroke patients from observational epidemiological studies before suggesting a possible pharmacological manipulation of the complement system in stroke.

The complement system has an important role in innate and specific immune responses with functions that include the augmentation of the acute phase response.1 It can be activated via two reaction pathways: the classic pathway, which is triggered primarily by cell-bound immune complexes, and the alternative pathway, which is activated primarily by foreign bodies, such as microorganisms. The complement component C3 is a key protein in both reaction pathways, whereas C4 belongs to the classic pathway of complement activation. Complement activation is associated with consumption of components of C3 and/or C4 so that a reduction in their concentrations can allow diagnostic conclusions to reached. In the presence of an inflammatory response, both complement components react as acute-phase proteins and may therefore show elevated serum concentrations. Unfortunately, our group and I do not have exhaustive epidemiological data on complement activation in ICH, but I would like to present to you our preliminary results on complement system in ischemic stroke.

Previously, our group found a strong inflammatory response after ischemic stroke detected by circulating levels of C-reactive protein (CRP).3,4 CRP increases in patients with ischemic stroke,3 may remain elevated after stroke, and is correlated with clinical outcome.4 Furthermore, CRP is also able to activate the classic pathway of complement.5 These data also encourage the study of the role of complement activation after ischemic stroke.

From this viewpoint, I have recently analyzed the data on complement activation in our previously described stroke cohort.3,4 We measured serum levels of C3c and C4 complement component together with CRP levels within 24 hours after stroke. Continuous variables are described as median value with 25th and 75th percentiles. Comparisons between groups were evaluated by the Mann-Whitney or Kruskall-Walliss test, when appropriate. To avoid possible confounding factors, no patients with evidence of possible elevations of inflammation markers due to other causes except for stroke were included in this series. A systemic complement activation was evident in only 30 patients (15.5%) within 24 hours after stroke. Median (25th to 75th percentiles) serum levels of C3c and C4 complement components and CRP were 1.32 (1.14 to 1.55) g/L, 0.31 (0.27 to 0.39) g/L, and 13 (6 to 33) mg/L, respectively, in 193 first-ever ischemic stroke patients. Log-transformed C3c levels were modestly correlated with CRP (Pearson correlation coefficient \( r=0.12, P=0.049 \)) and fibrinogen (\( r=0.25, P<0.0001 \)) levels, while C4 was correlated with fibrinogen (\( r=0.20, P=0.003 \)) but not with CRP (\( r=0.08, P=0.145 \)).

Significantly reduced median serum concentrations of C3c (\( P=0.0052, \) Kruskall-Wallis test) and C4 (\( P=0.0007 \)) were primarily observed in cardioembolic strokes when compared with atherothrombotic and lacunar strokes. In the case of cardioembolic stroke, the serum concentrations of the complement factors reflected the stroke severity (\( r=0.18, P=0.007, \) and \( r=0.22, P=0.001, \) respectively) assessed by Canadian Neurological Stroke Scale Score. Lower levels of C3c (\( P=0.0450, \) Mann Whitney U test) and C4 (\( P=0.0385 \)) were also significantly associated with the presence of leukoaraisosis (diffuse or patchy lucencies of the white matter or centrum ovale) and large infaracts (when the sum of the largest transverse and sagittal diameter divided by 2 was >1.5 cm, \( P=0.0468 \) and \( P=0.0408, \) respectively). Isolated increased C3 values (\( P=0.0101 \)) occurred in the presence of cortical involvement (>50%) whereas increased levels of C4 were found in spontaneous hemorrhagic transformation of the infarction (\( P=0.0403 \)). Apparently, the presence of edema did not induce an systemic activation of complement system within the first 24 hours after stroke.

Our preliminary results show a variable response of complement system after ischemic stroke. Prevalently, the complement activation in ischemic stroke occurs via the classic pathway. A systemic activation of the classic pathway in the first 24 hours after ischemic stroke is apparently present in cardioembolic stroke, in larger infarcts, and in the presence of leukoaraisosis. Thus, complement activation could be a key event mediating the deleterious effects of the local inflammatory response occurring in the infarcted area. The nature of the substances in the infarcted area that start activation of complement by binding and activating the first component of complement is unknown. However, our results indicate that CRP could be involved as an activator. Yet, we cannot exclude the possibility that other substances able to activate complement are generated in the infarcted area during the first 24 hours because we found only a modest correlation with CRP.

In conclusion, our data suggest that the activation of complement enhances inflammation and hence promotes more severe strokes. Moreover, these observations might have pathophysiological implications in ischemic stroke, because in other similar conditions, such as myocardial infarction, very similar responses are seen.6 Future studies to investigate the complement role in ischemic stroke are warranted.

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Response

We would like to thank Dr Di Napoli for his thoughtful letter. We agree with his comments about the difficulties in translating basic research on animals to the clinic and the need for further studies into the role of complement in brain injury. Our data and those of others suggest that complement does play a role in brain injury following stroke and in other similar conditions, such as myocardial infarction. Dr Di Napoli’s data are intriguing in providing data indicating that complement system activation occurs in human stroke as well as in animal models. As he points out, human stroke is very heterogeneous, and this variability may account for differences in the degree of complement activation seen in his patients. It should also be noted that measurements of systemic complement activation may not fully reflect complement activation within the brain. One of the advantages of performing animal experiments is access to brain tissues to assess such activation. Indeed, we have found that complement C9 protein content is increased in the brain after middle cerebral artery occlusion in rats.

Finally, we would encourage him and his colleagues to look at evidence for complement activation in his patients with intracerebral hemorrhage. Apart from the results presented in our article, there is evidence that there is a greater inflammatory response after intracerebral hemorrhage compared with ischemic stroke, and the direct influx of blood components into brain after an intracerebral hemorrhage may be a particularly potent stimulant of complement activation.

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Venous Thromboembolism After Acute Stroke

The recent review by Kelly et al generally takes a balanced view of the evidence cited but surprisingly omits some very important evidence.

There is good evidence from several sources that antplatelet agents (most of the evidence comes from trials of aspirin) are effective and safe in preventing deep venous thrombosis (DVT) and pulmonary embolism (PE) in a wide variety of patients at high risk of venous thromboembolism. A systematic review of the randomized trials available up to 1994, including a total of approximately 9000 patients, showed that antplatelet agents (chiefly aspirin) significantly reduced the risk of DVT by 39% and PE by 64%. Some clinicians were not persuaded by the evidence from the Antplatelet Trials’ meta-analysis, so a large-scale trial was established to confirm or refute these results. The Pulmonary Embolism Prevention (PEP) trial sought to evaluate the effects of low-dose aspirin in the prevention of pulmonary embolism and deep vein thrombosis in patients undergoing surgery for hip fracture. The trial randomized 13,356 patients to aspirin or placebo. Allocation to aspirin significantly reduced the odds of PE by 43% (95% CI 18 to 60) and symptomatic DVT by 29% (95% CI 3 to 48).

The Cochrane review by Gubitz et al (not cited by Kelly) identified 8 trials of antplatelet therapy in patients with acute ischemic stroke that reported effects on venous thromboembolism. Only 2 trials (including just 136 patients) reported effects on DVT; allocation to antplatelet therapy produced a nonsignificant 22% reduction in the odds of DVT (95% CI 64% reduction to 67% increase). However, 8 trials with 40,872 patients (chiefly Chinese Acute Stroke Trial [CAST] and International Stroke Trial [IST]) reported effects on PE; allocation to aspirin significantly reduced the odds of PE by 29% (95% CI 4 to 47%)( χ2 P = 0.03). Taken with the evidence of benefit in other categories of patient, and given the established safety of aspirin in stroke, it seems reasonable to conclude that aspirin does reduce the risk of DVT and PE after stroke. For patients with ischemic stroke, aspirin has many advantages as first-line agent for thromboprophylaxis: it is inexpensive, needs only once-daily administration, does not require injections, and is associated with a low risk of bleeding. The research question is now, can heparin add to that benefit? Any new trial would, therefore, need to compare aspirin alone with aspirin plus low-dose heparin and would need to recruit perhaps a few tens of thousands of patients to answer the question reliably (since PE appears to be uncommon after stroke these days).

One other small omission. We agree with Kelly that the value of graded compression stockings (and the choice of full-length or below-knee) for the prevention of DVT and PE after stroke is not well established. A Cochrane review on this topic is in preparation. Furthermore, the Scottish Executive has just funded the Clots in Legs or TED Stockings (CLOTS) collaborative group to undertake a multicenter, randomized, controlled trial to evaluate the benefit of graded compression stockings after stroke; the study is a small “family” of 2 trials, one comparing long stockings with no stockings and the other long stockings with short stockings. Details of the protocol are available at the trial website (www.dcn.ed.ac.uk/clots).

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References

Response

We are grateful to Prof Sandercock and Dr Dennis for their valuable comments. The currently recommended thromboprophylactic strategy after acute ischemic stroke is combined early use of aspirin and graded compression elasticated stockings (GCS).\(^1\) Although the reduction in risk of PE seen with aspirin in the IST\(^2\) did not achieve significance, we do agree that accumulated data suggest that aspirin is effective in these patients, with a risk reduction of 29% demonstrated in a recent Cochrane review.\(^3\) However, aspirin has not been shown to reduce overall mortality in surgical patients,\(^4\)\(^5\) and the marginal effect on early mortality after stroke has been predominantly attributable to prevention of recurrent ischemic stroke.\(^2\) GCS reduce DVT in surgical patients by about two thirds,\(^6\) although there are insufficient data to assess their effect on PE and total mortality. Although it seems reasonable to assume that they may also prevent DVT after stroke, this has not yet been clearly demonstrated.

By contrast, an overview of 70 trials of unfractionated heparin in some 16,000 general, orthopaedic, and urological surgery patients has shown a two-thirds reduction in fatal PE and reduced total mortality,\(^7\) and low-molecular-weight heparin is at least as effective.\(^8\) Moreover, heparin is also commonly combined with an alternative thromboprophylactic modality, usually GCS.

The incidence of PE in the IST\(^2\) in aspirin-treated patients who did not receive heparin was only 0.7% at 2 weeks. However, these data do not reflect the overall importance of PE as a cause of early morbidity and mortality, because fatal pulmonary emboli rarely occur in the first week after stroke, being most common between the second and fourth weeks.\(^9\) In addition, pulmonary emboli were not systematically sought within this period and were therefore probably underascertained, particularly given that the notorious propensity to underdiagnose or misdiagnose this condition is compounded in a population in whom dysphasia, confusion, and obtundation are common. Even in the IST, though, PE accounted for approximately 20% of early nonneurological deaths and 8% of all early deaths, and other studies have indicated that PE causes up to 25% of early deaths.\(^10\) Clearly, although the absolute risk of fatal PE after stroke is small, it is still an important cause of early mortality.\(^9\)

Given that the prevalence of DVT after stroke is greater than that after general surgery and similar to that following knee arthroplasty\(^11\) and that venous thromboembolism (VTE) is potentially the most preventable and treatable of poststroke complications, the following question logically arises: are we doing enough to minimize VTE-associated morbidity and mortality after stroke?

Arguably, a further trial of low-dose, low-molecular-weight heparin for a period greater than 2 weeks and with a more systematic evaluation for VTE would be justified but would require large numbers of patients to demonstrate improvements in clinical end points, as Sandercock and Dennis state. In addition, the results of the forthcoming multicenter trial evaluating GCS after stroke will be awaited with great interest. However, in the absence of further data, we suggest that research might profitably be directed toward evaluating a strategy of screening for subclinical DVT, as treatment in selected cases may improve outcome. In our own unit, we are investigating the hypothesis that plasma d-dimers might be a useful discriminator of poststroke DVT status, potentially allowing identification of a patient subgroup with a high risk of proximal DVT who should be selectively imaged. We are also prospectively assessing the true prevalence of PE (clinical plus subclinical) in these patients with magnetic resonance direct thrombus imaging. While a number of studies have reported on the frequency of clinical PE, subclinical events are likely to be considerably more common,\(^12\) and their prevalence in unselected patients is currently unknown.\(^13\)

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Re: Cost and Outcome of Mechanical Ventilation for Life-Threatening Stroke

To the Editor:

We read with great interest the article by Mayer et al\(^1\) regarding the cost-effectiveness of artificial ventilation (AV) in patients with acute ischemic stroke. We have recently published a prospective study concerning prognostic factors in patients with stroke who needed AV.\(^2\) We included an unselected group of stroke patients admitted to our department. In agreement with the finding of Mayer et al\(^1\) and others,\(^3\) approximately 10% of our patients needed AV (16/162), and a low overall survival rate (16/162) was noted. High scores on the National Institutes of Health Stroke Scale (NIHSS) on days 1 and 7 after the index stroke were identified as markers for the need of AV implementation. The day 7 NIHSS score was also the most powerful determinant of survival among ventilated patients (12.4±1.5 versus 19.5±4.2 for survivors versus nonsurvivors; P=0.003). Similarly to the report by Mayer et al\(^1\), we also noted very poor outcome in patients who needed AV for neurological worsening. However, unlike in previous reports,\(^4\) we were able to identify a subgroup of ventilated stroke patients who had good outcomes. The survival rate of patients who needed AV for cardiopulmonary decompensation (CPD) was 40%. These patients were discharged with moderate disability (Glasgow Outcome Scale score of 2 to 3 and NIHSS score of 8.7), albeit after a prolonged hospitalization compared with...
nonventilated patients. Furthermore, their neurological status continued to improve with time, although it was still lower than in the patients who did not need AV at all. The good outcomes observed in these patients preclude conclusive statements regarding the grim prognosis of all patients with ischemic stroke who need AV.

In conclusion, while the prognosis of intubated stroke patients is guarded on the whole, the chances for good recovery of patients intubated for CPD during their acute stroke hospitalization are significantly better than those of patients intubated for neurological deterioration. The high costs of prolonged hospitalization in this subgroup of patients appears to be rewarding not only in extending life but also in preserving quality of life.

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Response
We thank Drs Leker and Ben-Hur for their comments regarding our article. As we have pointed out, there is a need for more precise data regarding the prognosis of mechanically ventilated stroke patients. The more reliable these data are, the easier life decisions.

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Effect of Contralateral Occlusion on Long-Term Efficacy of Endarterectomy in the Asymptomatic Carotid Atherosclerosis Study (ACAS)

To the Editor:
We read with interest the article of Baker et al on the effect of contralateral occlusion on long-term efficacy of endarterectomy in the Asymptomatic Carotid Atherosclerosis Study (ACAS). The authors conclude that endarterectomy in asymptomatic patients with contralateral occlusion provides no long-term benefit (and may be harmful) in preventing stroke and death. The ACAS study established that the long-term risk of ipsilateral stroke in neurologically asymptomatic patients with a ≥60% carotid stenosis by ultrasound was reduced by carotid endarterectomy. The estimated 5-year risk for ipsilateral stroke was 11% for the medical arm and 5.1% for the surgical group, with a 53% relative risk reduction. The authors did a subgroup analysis of 163 participants with contralateral occlusion, 77 of whom were randomized to medical management and 86 to surgical therapy. The 5-year event rate was 3.5% for medical management and 5.5% for surgical management, with a 2% increase in absolute risk with surgery.

Previous evidence from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) has shown that patients with a contralateral occlusion were more than twice as likely to have an ipsilateral stroke at 2 years than patients with patent contralateral arteries. Cote et al also reported a stroke rate of 5% per year distal to an occluded ICA artery. Thus, the authors’ finding is in contrast to established literature. The authors speculate that collateral circulation may be the explanation for this difference. The authors suggest that since NASCET patients were asymptomatic, they likely had poor collateral circulation, and asymptomatic ACAS patients had better collateral circulation protecting them from stroke over time. There is, however, no literature supporting this speculation.

The ACAS study used ultrasonography to determine carotid stenosis, and several studies have now reported that a potential source of error in using these measurements is that the presence of severe contralateral internal carotid artery stenosis or occlusion may artificially elevate the peak systolic velocity or frequency values used to quantify the degree of stenosis in the artery of interest. Henderson et al elegantly demonstrated that the redistribution of blood flow due to severe stenosis in a contralateral carotid artery may lead to artificially elevated values in the ipsilateral artery and lead to overestimation of stenosis. Thus, an alternative but more likely explanation of the results of Baker et al is that ACAS patients with contralateral occlusion had overestimation of the carotid stenosis in the ipsilateral artery, actually had substantially lower stenosis, and several studies have now reported that a potential source of error in using these measurements is that the presence of severe contralateral internal carotid artery stenosis or occlusion may artificially elevate the peak systolic velocity or frequency values used to quantify the degree of stenosis in the artery of interest. Henderson et al elegantly demonstrated that the redistribution of blood flow due to severe stenosis in a contralateral carotid artery may lead to artificially elevated values in the ipsilateral artery and lead to overestimation of stenosis. Thus, an alternative but more likely explanation of the results of Baker et al is that ACAS patients with contralateral occlusion had overestimation of the carotid stenosis in the ipsilateral artery, actually had substantially <60% carotid stenosis in the artery being treated, and were unlikely to derive any benefit with revascularization in the first place, as shown in previous trials with moderate stenosis. This would also be consistent with the benign long-term outcomes with medical management in these patients with only moderate (<60%) stenosis.


Letters to the Editor 1447
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Response

We wish to thank Drs Mukherjee and Yadav for their interest in our recent article showing a questionable benefit of surgery among those patients with contralateral occlusion. They suggest an interesting potential explanation for the observed difference: the possibility that ultrasound could be overestimating the extent of atherosclerosis among those patients with contralateral occlusion. If this is the case, the benefit of surgery may be less among the patients with a lower degree of stenosis. This interesting hypothesis can be examined by selecting the subset of patients who were eligible for the study on the basis of ultrasound alone and subsequently randomized to surgery, where they received an angiogram for determination of stenosis on the ipsilateral side. Since the angiogram was performed after the eligibility was established, this subset of the study participants offers an unbiased view of the potential for lower degree of stenosis among those with contralateral occlusion. Of these 411 patients, the average ipsilateral stenosis (±SD) was 71.6%±14.4% for the 365 patients without contralateral occlusion and 67.1%±14.4% for the 46 patients with contralateral occlusion. This difference did prove significant (P=0.044) and as such could potentially contribute to the observed differential effect of surgery among those with contralateral occlusion. However, this effect is relatively small (a difference of only 4.5% in mean percent stenosis between groups) and would not apply at all to the 647 of 1659 ACAS patients (39%) who were eligible on the basis of near-occlusion angiographic evaluation. Because any patients with lower-grade stenosis would be allocated equally to the 2 treatment groups, this explanation also makes the assumption that there are major differences in the efficacy of surgery by percent stenosis (which does not appear to be the case in the ACAS population). Finally, the excellent outcome of the ACAS medically treated patients with contralateral occlusion is very similar to the excellent outcome of the medically treated patients with near-occlusion in the pooled ECST, NASCET, and VA #309 data that were recently reported at the American Stroke Association 26th International Stroke Conference. All patients in this combined population had the degree of stenosis established by angiography, and as such differential reading of ultrasounds is not an issue. In that report, the risk of stroke or death increased to the maximum in patients at 90% stenosis, and then declined considerably in the near-occlusion group, so that patients with near-occlusions were at less than half the risk of stroke or death of patients at 90% stenosis. Similar to our speculation, Rothwell and colleagues suggested that the excellent outcome of medically treated patients with near-occlusion may be a product of their documented collateral circulation. ACAS, unlike this pooled analysis, could not make this comparison because angiograms were not performed in all patients. In conclusion, while it is possible that the slight difference in the average stenosis of those with and without contralateral occlusion (which exists among the subset of patients admitted to the study by ultrasound alone) could contribute to the effects we observed, it is difficult to conceive that this is the major factor.

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Diurnal Variation in Stroke Onset in Atrial Fibrillation
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