Re: Stages and Thresholds of Hemodynamic Failure

To the Editor:

We appreciate the opportunity to address several of the comments made by Nemoto and his colleagues regarding our prior work.

First, and most importantly, we would like to emphasize that measurements of oxygen extraction fraction (OEF) remain the most rigorously validated method for identifying stroke risk in patients with carotid occlusion. We must disagree with statements by Nemoto et al. that OEF is not predictive of stroke risk. This conclusion is not valid, as it is based on erroneous interpretation of our data.

Increased OEF is predictive of stroke risk. The St. Louis Carotid Occlusion Study (STLCOS) was a blinded, prospective study of cerebral hemodynamics and stroke risk in patients with complete occlusion of a carotid artery. In this study, we prospectively set as a threshold the outer limits of the range of left-to-right hemispheric OEF ratios observed in a group of 18 neurologically normal control subjects. This threshold was established prior to the examination of the PET and outcome data for the 81 patients with symptomatic carotid occlusion. Eleven of the 13 patients with ipsilateral strokes occurring during the follow-up period had increased OEF, as defined by this threshold. Increased OEF was found to be both a powerful and independent predictor of subsequent stroke by Kaplan-Meier and multivariate analyses. Our findings were corroborated by a second study by Yamauchi et al. It is important to recognize that OEF has been shown to be a continuous variable, using either absolute values or hemispheric ratios. Nemoto et al are critical of the OEF threshold we used for absolute OEF in our recent article published in Brain. They also note that high OEF, as defined as the upper limit of the 95% reference range, did not identify all patients with subsequent stroke. This is true if this highly specific but insensitive threshold is used. This does not allow the conclusion that OEF does not predict stroke risk, however. Once the original hypothesis that OEF is an independent risk factor for stroke has been proven prospectively, the choice of any particular threshold is arbitrary and depends on the desired sensitivity and specificity for the test.

The study in Brain was clearly identified as a retrospective review, as is true for all our publications since the initial publication of the prospective STLCOS data in 1998. The first sentence of the methods section in this article states, “The material for this analysis was drawn from a retrospective review of clinical and hemodynamic data...” It was not presented as a prospective study, as they state.

Second, Nemoto and colleagues propose the existence of a chronic, stable third stage of hemodynamic impairment beyond maximal autoregulatory vasodilation and increased oxygen extraction. This interesting new theory is not supported by any data. They do not provide any PET data demonstrating a progression from stage II to stage III, nor do they provide any outcome data to show that patients in stage III are at a high risk for stroke. Thus, this construct remains highly speculative. In the original schematic of Powers to which they refer, this region after maximal OEF elevation refers to acute stroke where OEF remains highly elevated for hours while CMRO2 gradually goes to zero.

Finally, the relationship between vasodilatory capacity and stroke risk is variable. Well-designed, prospective studies of stroke risk have reported both positive and negative predictive value for tests of vasodilatory capacity. We agree that there are many questions to be answered regarding chronic regional hemodynamic impairment in humans and that more research needs to be done. The physiological relationships of oxygen extraction fraction, cerebral blood volume, and vasodilatory capacity are complicated and as yet poorly defined.

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Diurnal Variance in Stroke Onset

To the Editor:

We were interested to read the article by Stergiou et al and response by Dr Bursztyn. The diurnal variation in stroke onset is of both practical and physiological interest. The hypothe-
esis that siesta may be associated with stroke suggests real changes in physiology. In Calgary, Canada, siesta is not practiced. We collected time of stroke onset, defined by the last-seen-well principle, for all strokes (n=538) admitted to Foothills Medical Center in Calgary over the calendar year 2000. Stroke onset times were grouped by hour. The Figure shows the raw data and a fitted polynomial regression curve for the number of strokes admitted to hospital by hour of onset. The curve showed a reasonable fit to the data using linear regression corrected for autocorrelation of residuals (P=0.035).

The 1700-h peak in stroke occurrence, seen in Athens, does not occur in Calgary, providing some observational evidence that siesta may be an important risk factor for stroke occurrence. Alternately and perhaps more likely, ethnocultural differences in stroke risk factors and behaviors, stroke type, primary preventative treatments, and other factors may influence the local diurnal variation in stroke onset.

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Response
The letter by Hill and Newcommon raises important points: It strengthens the observations that practice of the siesta may be associated with stroke1 by showing that where there is no siesta the afternoon onset of stroke is not seen. However, the authors say that “in Calgary, Canada, siesta is not practiced.” In Jerusalem, Israel, we were also surprised to find that about 30% to 35% of those referred for ambulatory blood pressure monitoring practiced the siesta.2,3 We learned, however, that detection is easier when subjects are implicitly questioned about the siesta. In older people,4 we found the prevalence of the practice among 70-year-olds is even more common, almost 61%. Stergiou et al1 report that among their ambulatory blood pressure data set, the prevalence of the siesta may be as high as 75% to about 90% in those over 70 years of age!

As the siesta emerges as an important risk factor, it should be looked for. Of course there are cultural and ethnic differences:

“Mad dogs and Englishmen go out in the mid-day sun
The Japanese don’t care to, the Chinese don’t dare to
Hindus and Argentines sleep firmly from twelve to one
But Englishmen detest a siesta”

—Noel Coward (1899–1973)

However, prejudice will not help identify those who sleep in the afternoon—only direct questioning will.

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Atrial Fibrillation, Stroke, and Acute Antithrombotic Therapy

To the Editor:
Hart and colleagues1 summarize data for patients with acute presumed cardioembolic stroke from some, but not all, trials studying antithrombotic therapy. We believe that it is appropriate to share relevant data from the Tinzaparin in Acute Ischemic Stroke Trial (TAIST) study, a large trial comparing subcutaneous tinzaparin (a low-molecular-weight heparin [LMWH]) at 2 doses (175 anti-Xa IU/kg daily, 100 anti-Xa IU/kg) and oral aspirin (300 mg daily given for 10 days).2 TAIST recruited a total of 1486 patients of whom 368 (24.8%) had stroke secondary to presumed cardioembolism; AF was present in 181 patients (Table 1 of Reference 2). Although it has been suggested that patients with cardioembolic stroke might benefit acutely from anticoagulation, we found no evidence of this with respect to recurrence during treatment or functional outcome at 6 months (Table).

When assessing the 2 trials together, which compared an LMWH with aspirin (TAIST and HAEST3), LMWH did not benefit patients with presumed cardioembolic stroke: early recurrence, odds ratio 1.35 (95% CI, 0.72 to 2.61); death or dependency, odds ratio 1.18 (95% CI, 0.87 to 1.61).4 Similar findings were present in a meta-analysis of non-aspirin controlled trials of LMWH.5 Hence, it appears that LMWH do not reduce early recurrence in patients with AF or other causes of presumed cardioembolic stroke. We concur with Hart and Pearce that “early aspirin therapy is sensible” in such patients.1

Nevertheless, the subsequent statement that low-dose subcutaneous heparin can be added for the “prevention of venous thrombosis if substantial leg weakness is present”1 can be questioned. While LMWH undoubtedly reduce the incidence of venous thromboembolism (VTE, deep vein thrombosis and/or pulmonary embolism),6,5 VTE is now uncommon (2.6% in aspirin-treated patients in TAIST)3 while heparin has real costs: safety (hemorrhage), time (pharmacy, nursing, medical) and financial (drug). We now need a controlled trial to assess the

Events by Intention-to-Treat in Patients With Presumed Cardioembolic Stroke in TAIST

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recurrent Ischemic Stroke (or Unknown)</th>
<th>Good Outcome (mRS&lt;3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinzaparin (high dose)</td>
<td>134 (6.4%)</td>
<td>33 (25.4%)</td>
</tr>
<tr>
<td>Tinzaparin (medium dose)</td>
<td>121 (6.6%)</td>
<td>22 (18.8%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>112 (2.1%)</td>
<td>32 (29.1%)</td>
</tr>
</tbody>
</table>
Anticoagulation Uptake in Emergency Department Patients With Atrial Fibrillation

To the Editor:

Scott et al report that atrial fibrillation (AF) is commonly seen in emergency department patients and antithrombotic prophylaxis was suboptimal, despite the well-established benefits of thromboprophylaxis in AF.

The data reported by Scott et al are not altogether unexpected, and we are pleased that they have confirmed our previous observations. In 1994, we reported that AF was present in 6% of acute medical admissions to a Scottish district general hospital, and there was a suboptimal application of standard investigations for AF and a poor provision of thromboprophylaxis. Indeed, of the 102 patients presenting with known AF in a 6-month period, only 20% were taking warfarin and 17% were on aspirin, and of those not on warfarin only 34% had contraindications. These observations were confirmed in a multiethnic population in Birmingham, England, where only 28% of the 103 patients with previously known AF were already anticoagulated. The latter study also highlighted ethnic differences in associated etiological factors associated with AF, with hypertension being a common underlying cause of AF in Afro-Caribbeans, while ischemic heart disease was common among Indo-Asians.

Nevertheless, the improved, but still inadequate, rates of anticoagulation for AF reported by Scott et al (40% of the 556 patients with a history of AF), may be the result of more widespread recognition of the need for anticoagulation in AF. Of additional concern is their finding that of those patients on warfarin, 61% were outside the recommended target range of INR of 2 to 3, suggesting that even those who receive warfarin may not have their anticoagulation adequately managed. This complements our recent observations that many patients possess very limited knowledge of AF as well as its consequences and therapy. In particular, we have highlighted significant differences between different ethnic groups in terms of their knowledge of the risks, actions, and benefits of warfarin as well as AF itself.

The study by Scott et al also poses the question whether the emergency department provides the best setting to correct the apparent deficit in AF management. In our general practice survey, less than one third of patients with AF had ever presented to hospital practice, suggesting that the identification of AF patients who would benefit from anticoagulation should, for the most part, be encouraged in the primary care setting, where the majority of AF patients are actually managed. It is likely that in the emergency department, warfarin initiation would only contribute a relatively small amount to actually increasing the number of AF patients receiving warfarin.

Furthermore, a survey of Accident and Emergency Department (the equivalent of the “emergency department” in North America) consultants in the United Kingdom revealed a general reluctance to initiate oral anticoagulation in AF, with 51% stating that they would not do this routinely in an acute presentation. Our observations would suggest that there may be significant limitations to the initiation of anticoagulant therapy in the emergency department setting, at least in the United Kingdom.

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Response

We appreciate Drs Freestone and Lip bringing our attention to the disagreement regarding the prevalence of atrial fibrillation and the use of antithrombotic prophylaxis in Great Britain and agree that work remains to improve care in this at-risk population. We disagree, however, with the statement that emergency departments (EDs) could likely make only a small contribution to increasing the number of patients on warfarin. Although the EDs may not be the point at which to start outpatient anticoagulation (and this remains to be established) our findings clearly indicate a significant potential for ED identification of untreated patients and initiating care—either through referral mechanisms or direct physician contact—to increase antithrombotic use. It is likely the yield of such an approach will be substantially different in the United States given the marked differences in health care delivery between the two countries.

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Potential Pitfalls in Applying Carotid Endarterectomy Perioperative Mortality and Morbidity Rates

To the Editor:

Recent guidelines for carotid endarterectomy (CE) recommend a requirement for very low perioperative complication rates (≤3.0%).¹ For symptomatic patients, with 70% to 90% stenoses, however, a CE stroke perioperative complication rate of 6.0% is likely to show a 16.5% decrease in risk for nonfatal stroke or death at 2 years.² The 2 major trials, the NASCET² and ECST,³ had perioperative complication rates of 5.8 (95% CI, 3.3 to 8.3) and 9.1% (95% CI, 6.1 to 12.0), respectively. There was no significant difference between CE complication rates for the 2 trials (P=0.14), and the NASCET rate is significantly higher (P<0.01) than the present recommendation of 3.0%. The importance of the CE complication rate, with respect to any net patient benefit, has prompted calls for the routine availability of relevant data on both surgeons and hospitals. This is particularly relevant given comments that CE perioperative complication rates quoted for published studies may be atypically low due to a reporting bias, and that analysis of Medicare data finds CE 30-day complication rates that range between 5% and 11%.⁴

If we assume that the true underlying rate for CE perioperative complications is 6.0%, and that figure would ultimately be achieved by an institution, if it performed a large enough series of CE procedures (n=1000), the expected range of perioperative complications, in smaller random samples, can be calculated using a technique referred to as Monte Carlo sampling.⁵ Accordingly, when the recommended sample size of 100 is used, the results show that only perioperative complication rates ≥10% are statistically distinct (P<0.05, 1-tail). Thus, within an institution, CE complication rates of ≥7%, based on small sample sizes, are likely to occur about 40% of the time, even though the true, but as yet undefined, CE perioperative complication rate is 6%. Alternatively, if the true institution CE complication rate is 10%, identical calculations establish that approximately 19% of all samples will have a rate ≤7%. These findings challenge the present assumption of predicting future CE complications rates, based on retrospective small sample analyses.

Although the NASCET and ECST trials provide some information about the risks and benefits of CE, considerable uncertainty still persists on how to effectively advise individual patients about the potential risks and benefits at any single institution. Moreover, one study found that 20% of surveyed physicians were unaware of the existing CE complication rates, while 20% of accredited surgery residence programs acknowledged a failure to implement any form of systematic CE audit.⁶ Notwithstanding these latter limitations, it has also been previously reported that patients rarely conceptualize interventions, such as CE, as a straightforward question of risk reduction.⁶ In summary, if the absolute benefits of CE are dependent on accurate data concerning the perioperative complication rate, then for many individual patients appropriate clinical advice as to the risk versus benefit trade-off cannot be reliably provided.

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3. The European Carotid Surgery Trialists’ Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. Lancet. 1991;337:1235–1243.
Potential Pitfalls in Applying Carotid Endarterectomy Perioperative Mortality and Morbidity Rates
Stephen Fitzgerald and George Phillipov

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