Obstructive Sleep Apnea as an Independent Risk Factor for Stroke and Mortality

To the Editor:

In a recent article by Hu et al., the authors stated that both hypertension and type 2 diabetes were independently associated with an increased risk for stroke and stroke mortality. Indeed, the association of hypertension and type 2 diabetes conferred the highest risk, being higher than that attributable to each disorder separately.

We would like to remark on the possible role of obstructive sleep apnea (OSA) as one other possible factor contributing to the incidence of stroke and stroke-related mortality in their study population. OSA is characterized by intermittent episodes of partial or complete obstruction of the upper airway during sleep that disrupts normal ventilation and sleep architecture and is typically associated with snoring and daytime sleepiness. This primary sleep disorder affects 17% to 24% of North American adults, and is associated with a group of proinflammatory and prothrombotic factors that have been identified to be important in the development of atherosclerosis. On the other hand, OSA is now recognized as an important identifiable cause of systemic hypertension, and in patients with established type 2 diabetes, a significant relationship between OSA and fasting insulin, glucose, and hemoglobin A1c, levels, that is independent of obesity, has been reported. A strong association between OSA and the risk of stroke or death has been established, and that association is independent of a broad range of other cardiovascular risk factors. In view of the aforementioned data it is conceivable that part of the risk of stroke assumed to be attributable to hypertension or type 2 diabetes might be attributable to OSA.

Response:

We appreciate Arias et al for their comments on the potential role of obstructive sleep apnea (OSA) as another possible factor contributing to the incidence of stroke and stroke-related mortality in our results. We agree with their comments that OSA is an important health problem and seems to be an independent risk factor for the development of hypertension, and may increase the risk of stroke or death from any cause. Unfortunately, attributable to a very large sample size, we were not able to collect information about the diagnosis of OSA at baseline or during the follow-up. However, the role of OSA and other sleep disorders in the development of diabetes and cardiovascular diseases is an interesting question with a potential public health importance and needs to be considered in future studies.

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glucose levels after acute stroke can modify clinical outcome. The United Kingdom Glucose Insulin in Stroke Trial (GIST-UK) was designed to address this question, using an intravenous glucose-potassium-insulin (GKI) infusion to induce and maintain euglycemia.1

We are disappointed that Garg and colleagues chose to dispute the relevance of the results of GIST-UK before its completion and without appropriate interpretation of the trial protocol. The final patient will be randomized March 31st, 2006, and the results should be available for presentation and publication in early 2007. Garg’s article reflects a basic misunderstanding of the trial methodology and its context. The aim of GIST is to determine the effectiveness of intervention to maintain euglycemia in routine practice. Although guidelines may currently exist for the management of hyperglycemia, there is no evidence to suggest such intervention is either effective or safe. With respect to target blood glucose levels for the control (saline) group, admission plasma glucose of 17 mmol/L represents the upper limit for inclusion in the trial, not target glucose level. The treatment arm of GIST has a target capillary glucose of 4.0 to 7.0 mmol/L, with the objective in the control group being not to intervene unless glucose rises above 17 mmol/L. The most recent published data from GIST demonstrates that the majority of randomized patients have only moderate hyperglycemia (mean admission plasma glucose 8.37 mmol/L).2 Furthermore, without specific intervention plasma glucose levels fall spontaneously in the control group. Thus, any suggestion that patients are being managed with glucose levels of 17 mmol/L is both misleading and incorrect. Our work has demonstrated the safety and efficacy of the GIST GKI regime in the maintenance of euglycemia after acute stroke and currently is the only evidence-based approach from which we can describe how poststroke hyperglycemia can be managed.

We designed the GIST GKI regime to be delivered as part of routine care to the maximum number of eligible patients. In the event of a simple, safe and effective treatment for stroke being discovered, it is probable this will be given to patients with significant levels of comorbidity and pre-existing disability. Thus, the currently favored end point in stroke treatment trials of ‘good outcome’ (modified Rankin Scale [mRS] <1 or <2) is not appropriate; the use of a ‘poor outcome’ as a clinical end point becomes much more relevant. The wish of most stroke patients is the avoidance of the ‘poor outcome’ of death or severe disability. We therefore elected to use mortality at 12 weeks as the primary outcome measure for GIST-UK. Furthermore, as a secondary outcome measure we dichotomized the mRS so that a 12-week mRS of 4 to 6 is categorized as a ‘poor outcome’.3 We estimate that given predicted final recruitment to GIST-UK, the trial will have sufficient power of 90% at the 5% level to detect meaningful differences in nonmortality outcomes between groups, as measured using the mRS. Avoidance of a ‘poor outcome’ reflects the findings of the Stroke Unit Trialists’ Collaboration (reduced dependency, institutionalization, mortality), supporting our belief that this end point is highly relevant.4

There are many issues that arise from clinical trial methodology, but it is inappropriate to dismiss the design and implementation of a trial based on inaccurate interpretation and before publication of results. We look forward to sharing the results of GIST-UK with the stroke research community in the near future.

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Response:

O’Connell and colleagues have raised several questions about our review1 while giving some new information about the GIST-UK. Safety data on GIST was published in 1999, and the trial was projected to end by 2002.2–3 It’s good to know that the last patient will soon be randomized and we are likely to see the results by 2007. We understand the GIST protocol to the extent it has been published. It is possible that that there is more to the GIST trial methodology than published so far. However, the fact remains that there is no intervention in the control group unless glucose rises above 17 mmol/L. If GIST were to be planned today, the threshold for intervention in control group will be much lower because the definition of conventional treatment has changed over time. Lower threshold for insulin treatment in the control group would have led to a bigger sample size. That’s why we suggest a nonmortality primary end point. Although we appreciate the effort to determine the effectiveness of insulin infusion in routine practice, it may be helpful to first establish the effectiveness in any setting. Insulin infusion is still not given outside the special units in most US hospitals. This is probably true of UK as well. Finally, no one can dismiss a major trial like GIST. We are eagerly waiting to see the results of this trial, as is the rest of the medical community. However, if it were to take several more years, a trial on the lines that we suggested in our review might have been worthwhile in retrospect.

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Repeated Tissue Plasminogen Activator Treatment for Early Stroke Recurrence: Protocol Violation Is Not an Option

To the Editor:

We read with interest and concern the article by Topakian et al1 in which the authors describe the clinical case of a stroke...
patient successfully treated with tissue plasminogen activator (tPA) that experienced a recurrence and therefore was treated again with a low dose of tPA 90 hours after the first event. Authors argued that the rationale for the second treatment was the "evidence of vessel reocclusion and profound perfusion/diffusion mismatch"; this statement raises several considerations.

The diffusion/perfusion (DWI/PWI) mismatch concept to select acute stroke patients suitable for reperfusion therapies is currently under investigation with promising expectations.\(^2,3\) However, this concept is being applied in patients who do not present subacute ischemic lesion, a major exclusion criterion in all to-date thrombolysis studies. Although DWI/PWI mismatch may represent a surrogate marker of potential salvageable brain tissue if rapid restoration of blood flow is achieved, its presence does not provide by itself safety information. Extent and severity of cerebral ischemia are considered major determinants of symptomatic intracranial hemorrhage (SICH) in stroke patients treated with tPA. Several MRI studies have shown that the analysis of apparent diffusion coefficient maps but not the presence of DWI/PWI mismatch predicts the risk of SICH.\(^4\) Even relatively small but profoundly ischemic lesions may reflect areas of severe brain–blood barrier disruption and increased risk of SICH.\(^5\) Moreover, a late reperfusion of an already damaged brain tissue has been associated with a higher rate of SICH.\(^6\) Although a second IV thrombolytic bolus has been reported successful in patients with acute myocardial infarction,\(^7\) several pathophysiological-based safety concerns may preclude its use in patients with recently infarcted brain tissue.

Extension of the time window for reperfusion therapies represents a major goal for stroke treatment. We consider that development of novel approaches to increase the number of patients who may benefit from thrombolysis and reconsideration of some exclusion criteria such as recent ischemic stroke are encouraging. These studies, however, should always be done under strict protocols in order to acquire valuable information. Physicians should beware of isolated heroic measures that expose patients to noncontrolled risks without offering useful data for treatment improvement.

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**Response:**

Off-label use is no protocol violation. Managing early recurrent stroke represents a major challenge to stroke neurologists. For clinical settings like the one described in our article,\(^1\) clinicians will hardly find any evidence-based recommendation in current stroke treatment guidelines.\(^2,3\) In our patient, after the sudden dramatic neurological deterioration on day 4 attributable to an early recurrent stroke, we faced a difficult management problem.

Our decision to carry out a second recombinant tissue plasminogen activator (rtPA) treatment has nothing to do with heroism or “medical machismo,” as some may argue. Taking full responsibility for the consequences, we made our decision after carefully weighing up the arguments for risk and benefit of a second rtPA treatment. There were several arguments in favor of a second treatment with rtPA.

Firstly, we all know that the earlier thrombolysis treatment is started, the higher the chances are for neurological improvement.\(^4\) Obviously, the immediate recognition of the patients’ sudden deterioration by our stroke unit staff enabled us to consider another rtPA treatment with a relatively short stroke onset-to-treatment time.

Secondly, there was evidence of vessel reocclusion, a large perfusion deficit and a significant perfusion/diffusion mismatch, all demonstrated by multimodal MRI. Although the confirmation of vessel occlusion does not constitute a prerequisite for thrombolysis in current treatment guidelines, it certainly supports clinicians in their decision-making if the patient is considered for being given a potentially harmful thrombolytic agent.

Thirdly, we took account of the fact that the patient had already been receiving “best medical therapy” before the second stroke, ie, a platelet inhibitor (clopidogrel), an angiotensin-converting enzyme inhibitor (lisinopril), and a statin (simvastatin). Each of these medications is thought to have >1 beneficial effect in stroke patients, but our patient did experience a second stroke in spite of this seemingly “optimal” regime.

Fourthly, as we already stated in our article, we were well aware that repeat intravenous thrombolysis might carry a considerable risk of serious hemorrhage in previously infarcted brain. However, the infarcted area in the 24-hour FLAIR images after the first treatment was rather small. With respect to a presumed higher bleeding risk in case of another full dose of rtPA, the second treatment was carried out with a markedly reduced dose.

In clinical settings like the one described above, stroke neurologists are at a loss when it comes to evidence-based medicine. Time and again physicians face complex clinical situations and patient subgroups to which information derived from controlled clinical trials cannot be applied. It goes without saying that it is not the intention of a single case report to offer novel treatment options to the medical community. However, we may remind our critics that the description of a special case may shed light on difficult and still unsolved aspects of patient care and that case reports do constitute a part of the evidence pyramid.

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Statins and Stroke: Current Clinical Practice

To the Editor:

The role of statins on secondary prevention of stroke is not still defined. Though statins have demonstrated to reduce the relative risk of ischemic stroke by between 18% and 51% in patients with previous coronary heart disease (CHD) or high vascular disease risk, this is not clear for all stroke patients.1 An ongoing clinical trial, SPARCL, may clarify this issue.2

In order to examine the use of statins for individuals with recent stroke in our current clinical practice, we reviewed the medical records of patients with acute stroke admitted to the Department of Neurology of the Hospital de Valme, Seville, Spain, and the Department of Internal Medicine of the Hospital de la Merced, Osuna, Seville, Spain, for a 3-year period. We included 1087 patients. Nine hundred and ninety-three cases (91.4%) were ischemic infarcts and 94 (8.6%) hemorrhages. From these ischemic cases, 182 patients (18.3%) were taking statins when discharged. The main statins used were atorvastatin (34.6%), pravastatin (34.1%), simvastatin (30.2%), and lovastatin (1%). High cholesterol level was presented in 348 patients (35%); only 165 of these patients (47.4%) received statins at discharge. CHD was present in 173 patients (17.4%), but only 44 of these patients (25.4%) were taking statins at discharge. Previous stroke-transient ischemic attack and clinical limb-ischemia was present in 274 (27.5%) and 37 (3.7%) patients respectively, and received treatment in 21.5% and 24.3%. Age was associated with a reduced odds of receiving statins (P<0.001).

Our results show major deficiencies in the delivery of lipid-lowering therapy after stroke. Though statins have been shown to have beneficial effects in patients with stroke and known CHD and in other high vascular disease risk patients,1,3 and treatment strategies based on global cardiovascular risk have demonstrated to be most effective to prevent recurrent stroke and other vascular events,3,4 only approximately one-fourth of these high-risk patients received lipid-lowering agents by the time of discharge; thus, a high proportion of people who have acute stroke and coexisting cardiovascular risk factors are undertreated.

Therefore, while long-term statin trials for secondary prevention of stroke in the general population are expected to finish, clear major opportunities for secondary vascular prevention in patients with acute stroke are being missed.

Our findings reinforce the need to review the use of stains after acute stroke in our current clinical practice.

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Compatibility of Carotid Stenting and Cardiac Surgery

To the Editor:

We read with great interest the study by Randall et al1 describing their experience on carotid artery stenting before cardiac surgery. They present 19.2% combined minor stroke, major stroke and death rate, which appears to be higher than previously documented in the literature, as they admit.

The only published trial (investigation performed by the same authors)2 comparing dual antiplatelet regime versus aspirin alone for carotid artery stenting was prematurely interrupted for excess of benefit on the dual antiplatelet arm of the study, confirming the necessity of dual antiplatelet regime before, during and after carotid artery stenting. Stent endothelialization takes between 28 and 96 days.2 During this time the exposed metallic stent continues to act as a source of platelet activation2 so the dual antiplatelet regime benefits may be explained on the basis of the limitation of this phenomenon.

It is also well known that antiplatelet drugs increase bleeding complications during cardiac surgery, and dual antiplatelet regimes could increase furthermore the risk of bleeding in the perioperative period.

Consequently, in our opinion the 2 procedures are not compatible in their optimal version and compromise is inevitable. That is, the cardiac surgeon must decide to interrupt dual antiplatelet regime for the intervention to minimize bleeding complications, but increasing the risk of neurological adverse events, or perform the operation under dual antiplatelet regime reducing...
the risk of perioperative stroke, but increasing perioperative bleeding complications.

The third solution, the delay of the cardiac procedure to permit stent endothelialization and a less risky suspension of antiplatelet drugs was shown hazardous in their study, as they observed 3 deaths for cardiac causes (2 documented and 1 presumed) over a total of 52 patients pending for the operation.

In their study they state that the timing of cardiac surgery after stenting was at the discretion of the cardiac surgeon, but it would be very interesting to specify the mean time between the 2 procedures. We also believe that is of great importance to clarify if cardiac surgery was performed under dual antiplatelet therapy or they suspended 1 or both antiplatelet drugs in the perioperative period. This could explain the high rates of combined postoperative neurological adverse events.

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Response:

We would like to thank Drs Dalainas and Nano for their interest in our recently published article on carotid artery stenting before cardiac surgery. The points they raise in their letter highlight the need for the randomized trial we suggested, and we welcome the opportunity to expand on the points raised.

It is important to point out that the data presented in our article has been collected from our institution’s approved prospective carotid stenting registry of all stenting procedures performed by our radiologists. Therefore, our study methodology did not allow the minimum time between procedures to be stipulated at the outset of data collection. The limits of this methodology have already been discussed. In our series the earliest procedures were more likely to have been performed with only 2 weeks between the initial carotid stent and the subsequent cardiac procedure. However, in the majority of our cases, because of waiting lists in the UK for stable cardiac patients, the operations were >4 weeks apart. In the last 3 years all patients have had at least 4 weeks between the 2 procedures. This change was instigated once the benefits of dual antiplatelet therapy for a minimum of 28 days became clear.1

Problems associated with preoperative clopidogrel use and cardiac surgery remains a subject for much debate. Some studies have suggested that combined antiplatelet therapy increases the risk of cardiac surgery. However, a recent study has suggested that although dual antiplatelet therapy increases perioperative drain blood loss it did not result in an appreciable increase in reoperation rates or complications.2 There is also a growing body of evidence that dual antiplatelet therapy may reduce postoperative complications from off-pump cardiac bypass if started immediately after surgery.3 This is currently under study in a randomized controlled trial.4

In our original manuscript it was stated that almost universally our cardiac surgeons insist on stopping clopidogrel therapy 5 days before surgery, although more recently 2 operators have expressed a willingness to perform operations on clopidogrel if needed.

We agree that it may be shown by future trials that continuing treatment with staged carotid stenting and cardiac bypass surgery may prove incompatible. The need to continue the dual antiplatelet therapy for at least 28 days results in delays to cardiac surgery, which may increase the overall morbidity and mortality of this approach, negating the benefits obtained from the stenting procedure. However, what is not clear from our data are the number of adverse events prevented by this staged approach. It must be remembered that none of our patients undergoing carotid stenting experienced stroke or myocardial infarction at the time of stent insertion or immediate 24-hour follow-up. However, myocardial infarction at the time of carotid endarterectomy is a well recognized complication of staged endarterectomy and cardiac surgery.

What is clear is that the points raised can only be answered by a randomized controlled trial comparing cardiac surgery with prior carotid stent placement under dual antiplatelet therapy and cardiac surgery with no prior carotid intervention. We have been in discussion with investigators from London (Prof Martin Brown) and Leicester (Prof Ross Naylor) to perform a trial that it is hoped will answer this question.

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Compatibility of Carotid Stenting and Cardiac Surgery
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