Stages and Thresholds of Hemodynamic Failure

To the Editor:

Derdeyn et al 1 revisited their prospective study 2 on oxygen extraction fraction (OEF) by positron-emission tomography to predict stroke in patients with unilateral carotid occlusion. In it, they report for the first time that high OEF predicted increased stroke risk but only when combined with normal cerebral blood volume (CBV). High OEF with normal CBV did not predict increased risk for stroke. This observation is germane to the utility of cerebrovascular reserve (CVR) for the prediction of stroke risk. But first, we will comment on the stages of hemodynamic failure and the thresholds they chose to use in the prediction of stroke by OEF.

For the stages of hemodynamic failure, Derdeyn et al 1 chose to depict only stages I and II without stage III. Yet, it is well recognized that there is a stage III, as depicted by Powers 3 in his classic article on the relationship of the changes in cerebral blood flow (CBF), cerebral metabolic rate for oxygen (CMRO2), OEF, and CBV with a progressive fall in cerebral perfusion pressure. Stage III is important because many patients with chronic cerebral hemodynamic compromise present for care after they have suffered one, and often more, prior ischemic events. These patients frequently present with evidence of prior injury within the hemodynamically sensitive cortical and subcortical white matter. In this setting, CMRO2 should fall as would OEF, which is CMRO2 dependent. Thus, OEF increases in stage II but falls in stage III and is thereby biphasic as we have suggested (Figure). 4

Powers chose to show that OEF remained maximally elevated in stage III. However, the decrease in OEF with a primary reduction in CMRO2 has been described by several groups of investigators including Powers. 5–7 In our depiction of the different stages (Figure), we suggest that there is a decline in OEF in stage III, which provides a biphasic response in OEF with progressive hemodynamic failure. The problem created by this biphasic behavior of OEF is that in the absence of any other measure, OEF alone cannot differentiate between stages. On the other hand, CVR, unlike OEF, decreases progressively with hemodynamic failure of increasing severity.

In setting the threshold for the quantitative OEF values in the review by Derdeyn et al, 1 a value of 0.44 was used. The value of 0.44 was the upper limit of the 95% CI of the mean OEF (ie, mean +1.96×SEM) from 18 normal control subjects. It is inappropriate to use this value as the threshold to determine whether an individual OEF value is elevated or not. Rather, the upper limit of the 95% reference range (ie, mean +1.96×SD), which was 0.59, is the proper threshold. There is a distinction between the CI of the mean and the reference range. The CI of the mean refers to the estimate of the mean, while the reference range refers to the individual observation. Using the 95% reference range, only 3 of the 9 strokes were detected by OEF as opposed to 8 of 9 using 0.44. Therefore, contrary to the conclusions of the original publication, 2 high OEF alone is not a reliable predictor of stroke. If the 95% CI of the mean was used retrospectively to achieve a higher sensitivity, it should not be presented as a prospective study. It should also be noted that the label of the x-axis of Figure 4 in the article by Derdeyn et al 1 is not OEF in percent but rather fractional OEF.

Finally, the observation by Derdeyn et al 1 that high OEF combined with high CBV but not normal or low CBV predicted stroke is of interest. CBV should be related to CVR. In other words, as CBV increases, CVR decreases. In stage III, extreme compromise of CVR to negative values in regions dependent on pial collaterals from adjacent territories results in a true “steal” phenomenon. 8 However, CVR may also be reduced with normal or low CBV because CVR likely tests not only vasodilatory capacity but also vascular reactivity to a vasodilatory challenge. Thus, in stage III, reduced CVR may be the result of either reduced vasodilatory capacity or reduced vascular reactivity.

In summary, acceptance of OEF alone as the gold standard for hemodynamic failure is premature based on present data. A better understanding of the relationships between CVR and OEF and how they both relate to ischemic stress is needed.

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10. Kristeva R, Deecke L, Keller R, Kornhuber HH. Cerebral potentials preceding and transcranial magnetic stimulation (TMS) all have demonstrated sequential activation of the major folium of movement control in humans. It reflects the asymmetry of nature (ie, right hemisphere controlling the left) than that of a majority who do things in a reverse manner, also according to their own natural mandate.


12. Kristeva R, Deecke L, Kornhuber HH. Cerebral potentials preceding and transcranial magnetic stimulation (TMS) all have demonstrated sequential activation of the majority who do things in a reverse manner, also according to their own natural mandate.

13. Kristeva R, Deecke L, Kornhuber HH. Cerebral potentials preceding and transcranial magnetic stimulation (TMS) all have demonstrated sequential activation of the major hemisphere, all due to a diaschisis on the pathophysiology of acute stroke. Brain. 1983;106:197–222.


Response

We thank Dr Derakhshan for his interest in our article.1 We read his letter with great interest. We certainly agree that there is a hemispheric dominance of movement control in humans, and that this dominance may contribute to motor functional recovery after stroke. This hemispheric asymmetry can be observed not only during bimanual skilled movements outlined by Dr Derakhshan but also during simple unilateral hand movements. In normal right-handed subjects, simple left-hand movements elicit not only activation of the right (contralateral) primary sensorimotor cortex but also significant activation of the left (ipsilateral) primary motor area, whereas right-hand movements result in activation of only the left (contralateral) primary sensorimotor cortex.2,3 This asymmetry was not always evident in our control subjects, possibly because of individual variations or the threshold chosen for the statistical analysis. Thus, the primary motor cortex may play a role in ipsilateral hand movements, with the left hemisphere playing a greater role than the right. This functional asymmetry might lead to a greater chance for left hemiparesis to recover better than right hemiparesis. Therefore, we thought that it was more than by chance that the 6 patients selected in our study, who recovered excellently from massive infarction of the MCA territory, were all left-hemiparetic.

On the other hand, the extent of recovery from poststroke hemiparesis is highly variable, whether hemiparesis is right or left. There may be a number of reasons for the difference—not only the location and the size of the lesion, but also the individual variations in anatomic and functional connections. In this context, the individual variations of the proportion of crossed and uncrossed corticospinal tract fibers could partly account for the difference in functional recovery. As Dr Derakhshan quoted from Nyberg-Hansen and Rinvik,4 “there may probably be considerable variations with regard to the proportion of crossed and uncrossed corticospinal fibers in man.” And in addition, the authors mentioned the general norms in the same article: “75 per cent of all pyramidal fibers are usually said to course in the crossed lateral corticospinal tract, 10 per cent in the lateral uncrossed tract and the remainder in a ventral uncrossed tract.”

The pattern of cortical activation during paretic hand movements is very different from that induced during normal hand movements. Long-term functional recovery therefore may involve extensive reorganization of motor network within the brain, in addition to the recovery from acute reversible dysfunctions. When brain damage to the motor system is partial, recovery may be possible using the existing functional system or recruiting the adjacent cortical areas. However, when a motor system, such as the primary motor area, is destroyed, as in our cases, functionally related systems—such as the bilateral primary sensorimotor, premotor, and supplementary motor areas—need to substitute the function as an alternative if recovery occurs. Functional imaging studies have suggested that reorganization involving all of these areas may occur.1,5,7 In addition, learning (rehabilitation) may induce the formation of new synaptic connections.

Thus, there may be considerable options in producing the best recovery from stroke, although detailed mechanisms of recovery still remain to be elucidated. We have great interest in the ability of the adult human brain to adapt not only to environmental changes but also to lesion-induced reorganization throughout life. It is important to understand the mechanism of brain plasticity and possible ways to modulate it.

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Beneficial Effect of Albumin Therapy Attributable to α1-Acid Glycoprotein?

To the Editor:

Belayev et al1 report that albumin therapy has the beneficial effect of reversing stagnation, thrombosis, and corpuscular adherence in the cortical venules of a rat model of middle cerebral artery occlusion. They cite further studies in which human serum albumin treatment conferred neurological and histological protection in rat stroke models of focal2–4 and global5 cerebral ischemia as well as traumatic brain injury.6

We have previously shown7 that human α1-acid glycoprotein (orosomucoid), an acute phase protein, also has a beneficial effect in a rat model of global cerebral ischemia, even 30 minutes after reperfusion. In our study, human α1-acid glycoprotein was given IV in doses of 50, 200, and 600 mg/kg. Compared with control animals treated with placebo (albumin free of α1-acid glycoprotein), the doses of 200 and 600 mg/kg successfully mitigated brain edema.

The concentration of α1-acid glycoprotein in human plasma is about 0.2 to 1.4 mg/mL. One of its major physiological roles seems to be to maintain permeability of the capillary barrier,8 which is probably achieved by increasing the negative charge of the capillary endotheli- um9,10 and thus reducing the transvascular transport of polyanionic
macromolecules. Increased vascular permeability is a common symptom in various kinds of shock, stroke, etc. A beneficial effect of α1-acid glycoprotein can therefore be anticipated under these pathophysiologically conditions. Additionally, we have shown that resuscitation with human α1-acid glycoprotein effectively restores cardiac output and stroke volume in a rat model of hemorrhagic/hypovolemic shock11 by tightening the microvessel walls, thereby increasing the intravascular circulating volume.

During early posts ischemic reperfusion, there is a progressive accumulation of polymorphonuclear leukocytes in regions of low cerebral blood flow.12 It is known from in vitro studies with these leukocytes13,14 that α1-acid glycoprotein inhibits neutrophil aggregation and superoxide anion generation. Furthermore, α1-acid glycoprotein inhibits platelet aggregation15 and enables erythrocytes to pass through micropores,16 which probably improves altered rheologic conditions.

These studies in rat models of stroke point to the possibility that the beneficial effect of albumin treatment is attributable to the α1-acid glycoprotein content of albumin solution.

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Response
We appreciate the interesting response of Drs Muchitsch and Schwarz, describing the salutary properties of α1-acid glycoprotein in mitigating cerebral edema, combating abnormal increases in microvascular permeability, and inhibiting neutrophil aggregation. These investigators raise the intriguing speculation that the beneficial effect of albumin solution might be attributable to its α1-acid glycoprotein content. However, their own data would suggest that this is probably not the case: using the authors’ mean value of ~0.8 mg/mL for the concentration of α1-acid glycoprotein in human plasma (a value consistent with the published literature17) and a normal value for albumin in human plasma of ~4.4 g/dL, it follows that human plasma would be predicted to contain ~0.02 mg of α1-acid glycoprotein per mg of albumin. Our own previous studies1 show that human albumin is highly neuroprotective in focal ischemia even at 1.25 g/kg, ie, one-half the concentration of 2.5 g/kg used in the present study.2 According to the above computations, 1.25 to 2.5 g/kg of albumin would contain only ~25 to 50 mg/kg of α1-acid glycoprotein—a level far below the 200 to 600 mg/kg dose reported by these authors as required to reduce brain edema.3 The direct test of their hypothesis, however, would be the use of an albumin preparation free of α1-acid glycoprotein.

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Does Admission Body Temperature Predict Mortality After Acute Stroke?
To the Editor:
We read with great interest the recent article by Kammersgaard et al1 on the admission body temperature and prognosis after acute stroke. The conclusion is that low body temperature on admission is considered to be an independent predictor of good short-term outcome. The authors also concluded that the study suggests that admission body temperature seems to be a major determinant even for long-term mortality after stroke. The results are beautiful, and these conclusions are easy to be accepted in the light of many experimental studies showing the protective effect of hypothermia on the ischemic brain damage in the focal cerebral ischemia model (see a review2). However, we consider these conclusions possibly misleading.

An interesting article about body temperature in acute stroke was published in this journal3 from the same country just 1 year ago. Two of the authors (J.R., H.N.) of the present article belong to the same institute from which the previous article came. Although there might be some misunderstanding in some parts of the explanations,3 this study is epoch-making. Because Boysen and Christensen’s study has documented that body temperature in acute stroke can change very rapidly even within 6 to 8 hours after onset, a new paradigm is necessitated to study the relationship between body temperature and outcome in acute stroke. Six hours is too long
Letters to the Editor

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Response

We thank Drs Takagi and Fujimaki for their interest in our study on the effect of admission body temperature on long-term mortality after stroke.1 First, Drs Takagi and Fujimaki suggest that analyzing mortality for all patients admitted within 4 hours may be wrong. They furthermore suggest that patients should be stratified into smaller groups because body temperature changes during the early hours after stroke onset. In our study,1 body temperature was measured directly on admission to hospital. Of the total number of 390 patients considered, 278 (71%) were admitted within 4 hours and 118 (30%) within 2 hours after stroke onset. Drs Takagi and Fujimaki draw attention to the fact that body temperature may change after onset of stroke and vary between patients. This is an interesting issue, but our study was not designed to measure body temperature at different time points after stroke onset and that was not the aim of the study. We think that the only way to firmly conclude on the role for hypothermia in stroke treatment is to conduct randomized controlled clinical trials where body temperature is kept low for some time after stroke onset. Nevertheless, our study suggests that body temperature remains a strong independent predictor of long-term mortality, even after adjustment for other basic characteristics (eg, onset stroke severity, atrial fibrillation, and hypertension) that, unlike body temperature, a priori may be expected to continue to be a risk factor for mortality even after the acute phase of stroke.

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The ICH Score: Predicting Mortality and Functional Outcome in an Asian Population

To the Editor:

We were impressed by the simplicity yet apparent accuracy of the ICH scoring system proposed by Hemphill and coworkers.1 The score included factors that were found to be independent predictors of poor prognosis not only in their data set but in most other previously published studies as well. In response to their call for its validation in an independent cohort, Fernandes et al2 tested the score on 393 patients admitted to their neurosurgical unit in the United Kingdom. While ICH score was predictive of mortality at neurosurgical discharge, they felt that it was not as useful in predicting independent recovery because of a high rate of unfavorable outcome (severe disability, death, or vegetative state) even at a score of 2.

We were interested to see whether the proposed ICH score will prove valid in predicting not only mortality but also eventual functional outcome in our Asian population. Our local data show that intracerebral hemorrhage accounts for approximately 21% of hospitalized stroke cases. For the year 2001, we prospectively collected data on 302 patients with spontaneous ICH consecutively admitted to two major medical centers in the Philippines: the Philippine General Hospital and St Luke’s Medical Center. Data on 30-day mortality and modified Rankin scale (MRS) were complete in only 243 patients.

Infratentorial hemorrhage accounted for 12% of our cohort. Yet none of our patients scored 6. Only 3 patients scored 5 (1%), 18 scored 4 (7%), 28 scored 3 (12%), 52 scored 2 (21%), 70 scored 1 (29%), and 72 scored 0 (30%).

Overall 30-day mortality in our study was only 23%. The relationship between ICH score and 30-day mortality is shown in Figure 1. We likewise found the score to be predictive of poor functional outcome (MRS ≥4) at discharge and even more so at 30 days after discharge (Figure 2). This is in contrast to the results of Fernandes and coworkers who did not find the ICH score to be as helpful in this aspect maybe because they evaluated outcome too early at discharge without accounting for the eventual improvement in function over time.

Our results support the validity of the ICH score in predicting both mortality and eventual early functional outcome in our population. A subsequent analysis of functional outcome at a more meaningful time point, eg, 6 months, may be more revealing as suggested by Hemphill et al. As of the moment, however, one should observe caution in unintentionally using the ICH score in making treatment decisions. We propose that future investigations in the role of surgical interventions in intracerebral hemorrhage be stratified according to ICH score. Indeed, the results of such study will help standardize medical and surgical treatment protocols in intracerebral hemorrhage.
utilizing the ICH score for making treatment decisions in individual patients and assume that this implies that they did not introduce this source of bias into their prospective validation study. Interestingly, although their Figure 2 suggests that the ICH score may risk stratify functional outcome at 30 days as well, it also affirms that 30 days after ICH is probably too early to detect the level of improvement that is best assessed by functional outcome scales such as the modified Rankin Scale.

We appreciate that Jamora and colleagues have done what we could not: validate the ICH score in a group of patients geographically remote and culturally distinct from that of our original UCSF ICH cohort. This type of international critical appraisal of clinical grading scales and diagnostic tests is an invaluable way to advance collaboration in stroke. Perhaps more than anything, we hope that this ongoing dialogue about the ICH score has raised awareness and engendered enthusiasm for the daunting task ahead: finding an effective treatment for intracerebral hemorrhage.

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Re: Telephone Intervention With Family Caregivers of Stroke Survivors After Rehabilitation

To the Editor:

Grant et al.\(^1\) find that healthcare professionals are challenged to develop effective intervention programs that will assist family caregivers to effectively manage caregiver problems. It is possible these changes may have beneficial effects for stroke survivors who are indeed sensitive and reactive to caregiver coping behavior. Family members arranged to talk with the research nurse later in the day if they were busy with other activities. Perhaps this flexibility in rescheduling telephone contacts allowed caregivers to better focus and develop more rational problem-solving skills in addressing problems. This strategy is suggested by a report that pausing before taking action in stress management relative to usual care of mental stress–induced myocardial ischemia in men has substantial and immediate clinical and economic benefits. This hypothesis is supported by (1) the association of the reduction of blood pressure with longer, less recurrent speech hesitation pauses (about 2 seconds); (2) a report linking 3-second intertrial intervals with integration of target and body-part information in the premotor cortex when planning action; (3) the association of 2- to 4-second periods of rest with significant cognitive activity; and (4) a 2.5- to 3-second delay period for inhibition shaping neuronal activity and firing.\(^2,4\)

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Response

Dr Friedman was helpful in sharing empirical evidence from other studies regarding precise and objective methods that illustrate the value of pausing (in this case, rescheduling) before taking action in stressful situations, such as caregiving. How many times has each of us benefited from using this strategy to manage difficult situations and reduce anxiety?

Perhaps pausing is what we need to do in evaluating cost-effective interventions, such as the telephone. Dr Friedman cited literature that recognizes the telephone as a potential cost-effective strategy to use in addressing some problems experienced by patients and their families. As healthcare providers, all of us must examine the way we deliver care and continue to be creative in developing programs that assist family members to cope with the functional, cognitive, and emotional consequences of an illness such as a stroke, and help them to adapt therapeutic regimens to the realities of social, environmental, and familial demands. Using the telephone for health care professionals who talk with family members about their problems may be one strategy.

In evaluating intervention programs, investigators must evaluate not only statistical significance but also perceived clinical usefulness to research participants. In evaluating the usefulness of the intervention, family caregivers who completed the social problem-solving telephone partnership program were mailed a letter, asking them to tell us what they had learned by participating in the program. The participants’ responses were enlightening.

Participants reported they learned about stroke educational information, how to reach realistic and feasible goals, how to solve and deal with caregiving problems, how to plan for the patient, and how to handle the patients’ needs. Also, they learned how to put a problem into better perspective for a fast and accurate solution. In addition, the participants learned about themselves. The program showed them that there were people who cared about them and made them realize that they, as well as the stroke survivor, also were important, which made them feel good. They learned how to not be stressed out and how to solve their own problems. Moreover, the program helped them to be better caregivers.

These types of statements make all the months of grant writing and conducting research worth every second. Telephone interventions do not replace face-to-face contacts with health care professionals. However, they potentially can be used as an adjunct to improve the lives of stroke patients and their families and to meet some of their needs.

As regards the use of the HOPE trial, we fear that it is not appropriate to extrapolate its results to the kind of population the authors have studied because the baseline characteristics of the 2 studies are quite different regarding the prevalence of coronary heart disease, which was 80% in HOPE and only 15% in their cohort study, whereas the magnitude of stroke history prevalence was the opposite (11% and 100%, respectively). Cardiac death was therefore probably much more prevalent in HOPE (given that heart complication incidence was 5 times higher than that of stroke) than in their cohort study (for which the nature of death is not defined).

As regards the use of the PROGRESS trial, it is also not quite appropriate despite comparable baseline prevalence of coronary heart disease (CHD) (16% and 15%, respectively) and of stroke history (100%), because the stroke recurrence preventive effect of the ACEI perindopril per se was mainly related with its synergistic blood pressure (BP)-lowering action when given in association with indapamide, its own BP-independent stroke protective effect being even actually negative.

Indeed the PROGRESS trial is composed of 2 separate studies having independently randomized to placebo and to either perindopril alone or its association with indapamide, so the results of these 2 studies should be discussed separately, all the more that they are quite different. In the first study, perindopril alone did not significantly decrease the stroke recurrence risk (−5%) despite a 5-mm Hg SBP decrease, whereas in the second study its association with indapamide decreased it by 43% while the SBP decrease was 12 mm Hg. According to the PROGRESS authors, this BP decrease would account for a stroke recurrence risk decrease of only 33%. It seems therefore logical to ascribe the 10% BP-independent stroke recurrence protective effect of this association exclusively to its diuretic component. This interpretation is further supported by the comparison of the stroke recurrence risk decrease with indapamide alone in the PATS trial,8 also performed in patients with a history of stroke, which was 29% and not only 5% as with perindopril alone, while the SBP decrease was the same (5 mm Hg), so that the BP-independent stroke recurrence risk with perindopril comparatively with indapamide is 24% higher. Therefore, when the authors recommend ACEI on the basis of PROGRESS, it seems necessary that they add “in association with a diuretic.”

Considering the results of the recent clinical outcome trials with ARB, we propose that this latter class should also be considered, in preference to ACEI, especially in patients with a history of stroke associated with renal dysfunction. Indeed, this new antihypertensive class has been shown to have not only some BP-independent renoprotective effects9 as well as ACEI, but also BP-independent stroke protective effect in patients with low prevalence of CHD (<16%), whereas in these populations ACEI alone have been shown to be associated either with no BP-independent stroke protective effect1 or even with increased stroke risk.7 Indeed, the LIFE trial8 has demonstrated that an ARB like losartan decreases the risk of stroke by 25% compared with iso-antihypertensive dose of atenolol,8 while giving the same protection against cardiac complications. Furthermore, in the UKPDS 39 study,9 atenolol and captopril have been shown to have this same BP-independent brain and heart protective effect. Therefore it may be presumed that losartan has a greater BP-independent stroke protective effect than ACEI while having the same protective effect against cardiac complication.

We recognize, however, that our proposal urgently needs an actual formal demonstration by a direct head-to-head comparison of an ARB with an ACEI (in association with thiazide) in patients with a higher risk of stroke than of CHD as in populations with either a history of stroke...
(and normal or elevated BP) or of hypertension with high risk of stroke because of age or left ventricular hypertrophy as in LIFE but a low prevalence of CHD.

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Response

Prof Fournier et al’s contention that AT1-receptor blockers (ARBs) may be as good or better than ACE inhibitors (ACEi) may be true, but we know of no large trials in which ARBs have actually been given to stroke patients, whereas PROGRESS1 and HOPE2 represent, despite their imperfections, a large database on the effect of ACEIs in stroke survivors. This is why we recommended ACEIs in stroke survivors.

We accept contention by Fournier et al that ARBs are an exciting group of drugs and may also prove to have a protective effect on renal function. In a comparative study of 3 years’ treatment in hypertensive individuals, both enalapril and losartan did appear to reduce blood pressure, diminish left ventricular hypertrophy, and protect renal function.3 The losartan group also had a reduction of uric acid levels. We have shown recently that serum urate concentrations were associated with cardiac death after stroke, independent of many other risk factors, such as pulse pressure, glucose, cholesterol, and creatinine.4 This may partially account for the additional beneficial effect seen in the ARB group.

We would like to dispute Fournier et al’s belief that PROGRESS was in fact 2 separate trials.5 Patients were randomized to perindopril or placebo after an initial trial of tolerance of perindopril. The addition of indapamide was at the discretion of the investigator and was not controlled by a randomization process. Therefore, it is impossible to attribute the outcome differences to the effects of any particular treatment. The trial was powered only to demonstrate a difference between active treatment (perindopril or perindopril plus indapamide) versus placebo. The Post-stroke Antihypertensive Treatment Study (PATS)6 may give support to a diuretic effect in terms of end-point reduction but not renal protection. This study was in a Chinese population whose risk factors are possibly different from those of a Western population, and, importantly, the full results of this study have not been reported. It is not clear if thiazide diuretics are renoprotective. In UKPDS 39, captopril was associated with development of less proteinuria than atenolol, although the small numbers involved fail to reach significance.6 A meta-regression analysis in diabetic patients has shown that ACEIs are associated with a reduction in proteinuria compared with beta-blockers, although blood pressure control is similar.7

We agree that further studies may help clarify the respective roles in renal protection of ACEIs, ARDs, diuretics, and other antihypertensive medications in various groups of patients. These trials should include hypertensive and normotensive patients. We share the opinion of Fournier et al that a large comparative randomized trial examining the effects of the different classes of drugs is required in stroke patients to help clarify the position.

Currently the largest database on stroke patients and these drugs comes from the PROGRESS and HOPE studies, which give good support to the use of ACEIs in stroke survivors.

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