Stages and Thresholds of Hemodynamic Failure

To the Editor:

Derdeyn et al.1 revisited their prospective study2 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 Powers3 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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Why Nondominant Hand Movements Cause Bilateral Cortical Activation in Emission Imaging

To the Editor:

The contribution of Kato et al3 contains important laterality related data. But the respected authors resort to undocumented and unwarranted assertions from the literature that one must address in order to arrive at a cogent interpretation of their data.

They used the 1963 article of Nyberg-Hansen and Rinvik2 to support the existence of 10% to 15% uncrossed pyramidal fibers in humans. This article, which is often used for this very purpose, states that “the only safe conclusion to be drawn from the available data is that there may probably be considerable variation with regard to the proportion of crossed and uncrossed corticospinal fibers in man,” never offering or referring to such anatomical documentation in humans as asserted by Kato et al. On the other hand, the current techniques of cortical mapping with sufficient temporal resolution employing electrophenocaphalography, magnetoencephalography, and transcranial magnetic stimulation (TMS) all have demonstrated sequential activation of the major followed by the minor hemisphere on moving the nondominant hand (see below). This temporal feature of bimanual coordination in humans translates into such daily life experiences as (1) the double-click heard with snapping one’s fingers of both hands simultaneously (Derakhshian, unpublished data), (2) the melody lead of the right hand in piano playing1 (known to musicologists for 160 years), and (3) the precedence of the bowing hand to the fingering in violin playing, recently documented by Wiesendanger et al.4 This callously mediated delay of 10 to 40 ms involving the nondominant hand requires an anatomical explanation not forthcoming from the (unmodified) doctrine of contralaterality of movement control in humans. It reflects the asymmetry occasioned by a 1-way callosal traffic (underpinning all executive functions), manifesting the activating role of the neuronal ensemble located in the major hemisphere over its counterpart in the minor.5,6 The same is reflected in laterality indexed nondominant weakness after callosal transection (natural or iatrogenic) or in ipsilateral paralysis seen in lesions affecting the major hemisphere,7 all due to a diachisis on cessation of the activating influences mentioned earlier.8 This asymmetry, or laterality of movement control, is uniquely human, not seen in chimpanzees or other monkeys.9,10

Kato et al also refer to another report11 concerning an anatomic anomaly, ie, nondeossification of the pyramids in medulla oblongata, in the same vein of drawing unwarranted support for a conventional interpretation of their findings. The situation is indeed far more sophisticated and exciting than that depicted by the authors, as their data are in favor of the concept of directionality of the traffic from the major to the minor hemisphere in determining a subject’s neural (as opposed to ostensible) handedness.5,8

To recap: It is the major hemisphere that gears into action when any movement is willed, giving the contralateral dominant hand a head start equaling the interhemispheric transfer time (IHTT, measuring 10 to 40 ms). In the laboratory, the first acknowledgment of the precedence of the dominant over the nondominant limb came from Kristeva et al12 in 1979. Kristeva et al13 established the same in 1991 using magnetoencephalography, as did Chen et al14 in 1997, using TMS. Priori et al15 did the most elaborate study on both right- and left-handers, showing that the TMS-induced interruption of function lasted longer (by an amount equal to IHTT) on the nondominant side as the disrupting influence trailed along the callosum from the dominant to the nondominant side, arriving at the same conclusion as Chen et al, whose subjects were all right-handers. All those cited above have been silent as to the reason behind the finding, with occasional accusation of laziness on the part of the minor hemisphere by some16 or others who interpreted the result17 without any regard for the neurological syndromes adumbrated above and elsewhere.5,7

In this light, the right-handed patients and controls of Kato et al showed ipsilateral activation of the left hemisphere as they used their nondominant hand, as in numerous other studies they cited and many more16; none, however, were cognizant of the pathway that underpins the asymmetry of such findings, indexed as it is to the subject’s neural handedness: this pathway remains unchanged19 regardless of attempts to “convert” those wired for practicing according to a different mandate 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.

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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 outlined by Dr Derakhshan but also during simple unilateral hand movements. In normal right-handed subjects, simple left-hand movements (ipsilaterial 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.4 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.”4

The pattern of cortical activation during parietic 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 pathophysiological 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 shock 11 by tightening the microvessel walls, thereby increasing the intravascular circulating volume.

During early postischemic 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 leukocytes 13,14 that α1-acid glycoprotein inhibits neutrophil aggregation and superoxide anion generation. Furthermore, α1-acid glycoprotein inhibits platelet aggregation 15 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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**Hans Peter Schwarz, MD**
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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 literature a) 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 studies b 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. c 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. d 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 al 1 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 review 2). However, we consider these conclusions possibly misleading.

An interesting article about body temperature in acute stroke was published in this journal 3 from the same country just 1 year ago. Two of the authors (J.R., H.N.) of the present article 1 belong to the same institute from which the previous article 3 came. Although there might be some misunderstanding 4 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...
to treat as one group. The current article did not cite this important work and paid no attention to this point.

In Boysen and Christensen’s study, 725 patients were admitted within 6 hours of onset and were investigated. Fifty percent of the patients were admitted within 2 hours of onset. Mean temperature on admission of the patients who died within 7 days (36.5°C) or 3 months (36.5°C) tended to be lower than in survivors (36.6°C). In 93 patients, body temperature on admission was <36°C. These patients had more severe strokes than patients with higher temperatures did. Patients with body temperature >37.5°C on admission had better stroke scale than those with admission temperature ≤37.5°C did. These results are quite contrary to those from the article of Kammersgaard et al. We think this difference may come from the fact that Kammersgaard et al treated the patients admitted within 6 hours of onset as one group.

Boysen and Christensen’s study and our own study have demonstrated that 4 hours after onset of cerebrovascular diseases (cerebral ischemia, intracerebral hemorrhage, and subarachnoid hemorrhage) may be a turning point for the body temperature in the acute phase of these diseases. Therefore, we would like to know how many patients were admitted within 4 hours of onset in their study. We suspect most patients investigated in this study admitted 4 to 6 hours after onset.

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Response
We thank Drs Takagi and Fujimaki for their interest in our study of the effect of admission body temperature on long-term mortality after stroke. First, Drs Takagi and Fujimaki suggest that analyzing mortality for all patients admitted within 6 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, 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. 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 al 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 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.

Figure 1. The ICH score and 30-day mortality.
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 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 intratrial 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 activity.

These findings give precise, objective methods to facilitate problem-solving training and save travel time by remote acquisition of temporal features of expressive activity in spontaneous dialogues, reflecting neuronal activity and firing.

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To the Editor:

Thank you, Dr. Friedman, for your letter.

stroke patients and their families and to meet some of their needs. How-
not replace face-to-face contacts with health care professionals. How-

participants learned several things about themselves. The program

... tion, how to reach realistic and feasible goals, how to solve and deal

... they had learned by participating in the program. The participants

... responses were enlightening.

Participants reported they learned about stroke educational informa-

... how to handle the patients' needs. Also, they learned how to put a prob-

... 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. How-

... potentially can be used as an adjunct to improve the lives of stroke

... patients and their families and to meet some of their needs. Thank you, Dr. Friedman, for your letter.

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Converting Enzyme Inhibitor or AT1-Receptor Blocker for Decreasing Long-Term Mortality in Patients With Stroke History and Renal Dysfunction?

To the Editor:

Having concluded their cohort study with the suggestion that ren-

... al 2 strongly recommend the use of angiotensin-converting enzyme inhibitor (ACEI) to decrease this mortality. They base their recommendation on

the HOPE study, in which ramipril comparatively with placebo

... significantly decreased mortality in both patients with and patients without renal dysfunction, 2 and on the PROGRESS study. We think, however, that the use of the results of these 2 studies are not entirely appropriate for supporting this exclusive recommendation, alternative recommendation of diuretics and/or AT1-receptor blockers (ARB) having in our opinion at least equal or even greater evidence basis.

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 PROGRESS trial, 3 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 interpreta-
tion is further supported by the comparison of the stroke recurrence risk
decrease with indapamide alone in the PATS trial, 2 also performed in
patients with a history of stroke, which was 29% and not only 5% as
with perindopril alone, whereas 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 effects 3,4 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 effect 5 or even with increased stroke risk. 7 Indeed, the LIFE trial 8 has demon-
strated that an ARB like losartan decreases the risk of stroke by 25%
compared with iso-antihypertensive dose of atenolol, 9 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

1. Grant JS, Elliott TR, Weaver M, Bartolucci AA, Giger JN. Telephone intervention with family caregivers of stroke survivors after rehabili-
3. Constantinidis C, Williams GV, Goldman-Rakic PS. A role for inhibition in...
(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 AT 1-receptor blockers (ARBs) may be as good as 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 PROGRESS and HOPE 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 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. 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.

We agree that further studies may help clarify the respective roles in renal protection of ACEIs, ARBs, 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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Re: Telephone Intervention With Family Caregivers of Stroke Survivors After Rehabilitation
Ernest H. Friedman

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/34/1/7