take note of the methods that are used here for comparing model fit, discrimination, calibration, and the degree of reclassification among models containing different sets of covariates. It remains uncertain, however, whether Cox models represent the best method for the prediction of risk. Increasingly sophisticated partitioning and neural-network methods may ultimately make Cox-based prediction obsolete; if discrimination can be rendered near-perfect, calibration and reclassification become moot.

A close examination of the data for participants without prevalent cardiovascular disease indicates that the addition of the four biomarkers to the established risk factors resulted in a total of 133 appropriate and 69 inappropriate reclassifications. However, the clinical implications of these reclassifications are not clear. We do not know whether any action should or could have been taken to prevent the deaths from cardiovascular disease that occurred.

The analysis of Zethelius et al. suggests that combining selected biomarkers of cardiac and renal disease may improve the assessment of risk by established risk factors, at least among this unique cohort of elderly men. These findings need to be validated in younger cohorts of men and women that include only patients who are free from cardiovascular disease and should be updated iteratively as newer, and better, biomarkers emerge from discovery research programs. Then, the hard work begins in determining what should be done differently on the basis of the test results and in what format this complex information should be presented to clinicians.

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1. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
2. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791-8.
3. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 2007;115:928-35.
4. Lloyd-Jones DM, Liu K, Tian L, Greenland P. Assessment of C-reactive protein in risk prediction for cardiovascular disease. Ann Intern Med 2006;145:35-42.
5. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006;355:2631-9.
6. Shlipak MG, Fried LF, Cushman M, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA 2005;293:1737-45.
7. Zethelius B, Berglund L, Sundström J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med 2008;358:2107-16.
8. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med 2005;352:2049-60.
9. Galasko G, Lahiri A, Barnes SC, Collinson P, Senior R. What is the normal range for N-terminal pro-brain natriuretic peptide? How well does this normal range screen for cardiovascular disease? Eur Heart J 2005;26:2269-76.
10. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA 2005;293:1609-16.
11. Wallace TW, Abdullah SM, Drazner MH, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006;113:1958-65.
12. Latini R, Masson S, Anand IS, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007;116:1242-9.
13. Khera A, McGuire DK, Murphy SA, et al. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol 2005;46:464-9.
14. Chang AY, Abdullah SM, Jain T, et al. Associations among androgens, estrogens, and natriuretic peptides in young women: observations from the Dallas Heart Study. J Am Coll Cardiol 2007;49:109-16.

Intracerebral Hemorrhage — Improving Outcome by Reducing Volume?

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Intracerebral hemorrhage accounts for 10 to 15% of all strokes. It is the type of stroke with the highest mortality, with a 1-year survival rate of less than 50%.[1] Most intracerebral hemorrhages occur in patients who have hypertension, which is the major modifiable risk factor for the occurrence of intracerebral hemorrhage.[2]

Although improvements in the early recognition and general intensive care of patients with intracerebral hemorrhage have been associated

with decreased mortality, no specific intervention has proved efficacious. Mayer and colleagues, having previously reported encouraging results of a phase 2 trial in the *Journal*,[3] in this issue report disappointing results of the pivotal randomized trial of recombinant activated factor VII (rFVIIa) in the treatment of acute intracerebral hemorrhage.[4] Despite the failure to demonstrate a benefit, several important findings from this study suggest future directions for research and potential treatments.

Activated factor VII is indicated for the treatment of bleeding and for the prevention of bleeding during invasive procedures in patients who have congenital hemophilia with inhibitors to coagulation factor VII or IX, and for symptoms of bleeding in patients who have the rarer acquired hemophilia and congenital factor VII deficiency. Its use in patients who have cerebral hemorrhage and normal systemic coagulation to reduce hematoma extension is new.

Hematoma volume is a critical determinant of outcome in intracerebral hemorrhage, especially if measured early after the onset of symptoms. Extension of the intraparenchymal hemorrhage to the intraventricular space and the clinical condition of the patient at presentation, often represented simply by level of alertness, are other critical factors.[5] Growth of a hematoma, previously thought to be rare, is now recognized to occur to a clinically important degree in 38% of cases of intracerebral hemorrhage within the first 24 hours after the onset of symptoms; such growth is associated with increased mortality and poor functional outcome.[6] Preventing enlargement of a hematoma is therefore a logical pursuit in the treatment of acute intracerebral hemorrhage. Prevention of hematoma expansion is further supported by the results of the phase 2 trial conducted by these investigators.[3] In that trial, 399 patients with intracerebral hemorrhage diagnosed by a computed tomographic scan within 3 hours after the onset of symptoms were randomly assigned to receive placebo or 40, 80, or 160 μg of rFVIIa per kilogram of body weight within 1 hour after the scan. At approximately 24 hours, the mean increase in hematoma volume was 29% in the placebo group as compared with 16%, 14%, and 11% in the groups given 40 μg, 80 μg, and 160 μg, respectively, of rFVIIa per kilogram. This corresponded to reduction in the growth of the hematoma of 3.3 ml, 4.5 ml, and 5.8 ml, respectively. Mortality at 90 days was 29% in the placebo group but only 18% in the three treatment groups combined. In a separate analysis of 374 of these patients, intraventricular hemorrhage was present at baseline in 43% of the placebo group but in only 36% of the rFVIIa group. Growth in the volume of intraventricular hemorrhage occurred in 17% of the placebo group but in only 10% of the rFVIIa group,[7] suggesting a benefit of the treatment for the growth of intraventricular hemorrhage as well as intracerebral hemorrhage.

On the basis of these encouraging results, a definitive trial was initiated. A total of 841 patients were randomly assigned to received placebo or 20 or 80 μg of rFVIIa per kilogram within 4 hours after the onset of symptoms. Treatment with 80 μg per kilogram was associated with a significant reduction in the growth in volume of the hemorrhage, as compared with placebo (11% vs. 26%), corresponding to a moderate but statistically significant 3.8-ml reduction in the growth in volume as compared with placebo. Despite this, poor clinical outcomes occurred slightly more frequently in the treatment groups (24% in the placebo group and 29% in the group receiving 80 μg per kilogram). The investigators correctly point to the imbalance in intraventricular hemorrhage at baseline, present in 29% of the placebo group and 41% of the group receiving 80 μg per kilogram (an even larger disparity, but in the opposite direction, than was seen in the phase 2 trial), as a possible explanation for the failure to demonstrate clinical efficacy. The mortality rate in the placebo group was also markedly lower and the modified Rankin scale scores better than in the phase 2 trial.

What lessons can be learned from these experiences? First, doses of rFVIIa larger than 80 μg per kilogram increase the risk of arterial thrombotic events without a corresponding improvement in retarding hematoma growth; lower doses are not as effective. Second, randomization cannot ensure balanced groups, especially in trials of moderate size, and this in turn may affect results. Perhaps most important, these results emphasize two other principles that have emerged from other trials of stroke treatments: a single treatment approach may accomplish its physiological goal but may be insufficient to produce clinical benefit, and an intervention may be helpful to a well-defined subgroup but not to all

those who have a particular disease. The effects of advanced age, a large volume of intracerebral hemorrhage at baseline, and intraventricular blood may blunt the modest effect of limiting hematoma growth. Conversely, treatment closer to the onset of symptoms, when enlargement is more likely to occur, may have a greater effect.

An alternative experimental treatment may reduce the negative effect of extension of the hemorrhage into the intraventricular space. The administration of thrombolytic agents by means of intraventricular catheter has been shown to hasten clearance of blood from the ventricular system in phase 2 trials[8]; a definitive phase 3 trial is planned. This approach may achieve its goal of safely accelerating elimination of intraventricular hemorrhage but may have limited clinical effect or may prove useful only in the minority of patients who have relatively small intracerebral hemorrhages. It is possible to envision the potential benefit of a combination of these approaches by first limiting the size of the parenchymal hematoma with rFVIIa and then addressing the intraventricular component.

Reducing blood pressure may be a potentially more benign (and less expensive) approach to limiting hematoma growth. Initially thought to put the patient at risk for ischemic compromise of the tissue surrounding the hematoma, a moderate reduction in blood pressure has been shown to be safe. Current guidelines suggest a target blood pressure of 160/90 mm Hg or a mean arterial pressure of 110 mm Hg while maintaining cerebral perfusion pressure at 60 to 80 mm Hg.[9] Hematoma growth has been associated with higher blood pressures; a clinical trial examining the efficacy of blood pressure lowering in decreasing the risk of hematoma expansion is under way.

Other groups of patients, excluded from the current study, may be appropriate targets for enhancing coagulation. Warfarin-related hemorrhages tend to expand for a longer time than spontaneous hemorrhages. The most widely used approach currently uses fresh-frozen plasma and vitamin K and requires the administration of large fluid volumes, often without correcting the coagulopathy for several hours. More rapid correction with rFVIIa or a prothrombin complex concentrate has not been studied sufficiently to be recommended definitively.[9]

In summary, although failing to show a clinical benefit, the trials of rFVIIa in the treatment of acute intracerebral hemorrhage have demonstrated the ability of rFVIIa to limit hematoma growth while increasing the risk of arterial thrombosis only minimally, suggesting several possible avenues for further investigation. Other promising approaches to limiting hematoma growth or reducing hematoma volume are currently under study. Alone or in combination, these approaches may show a benefit. Proper selection of the patient group in which to apply these therapies may hold the key to these advances.

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1. Flaherty ML, Haverbusch M, Sekar P, et al. Long-term mortality after intracerebral hemorrhage. Neurology 2006;66:1182-6.
2. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med 2001;344:1450-60.
3. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2005; 352:777-85.
4. *Idem.* Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2008;358:2127-37.
5. Tuhrim S, Horowitz DR, Sacher M, Godbold JH. Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage. Crit Care Med 1999;27: 617-21.
6. Davis SM, Broderick JP, Hennerici M, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology 2006;66:1175-81.
7. Steiner T, Diringer MN, Schneider D, et al. Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage. Neurosurgery 2006;59:767-73.
8. Naff NJ, Hanley DF, Keyl PM, et al. Intraventricular thrombolysis speeds blood clot resolution: results of a pilot, prospective, randomized, double-blind, controlled trial. Neurosurgery 2004;54:577-83.
9. Broderick JP, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Circulation 2007;116(16):e391-e413.