Warfarin or aspirin for recurrent ischemic stroke [1] (multiple letters)

Correspondence

Warfarin or Aspirin for Recurrent Ischemic Stroke

To the Editor: The conclusions in the Abstract of the article by Mohr et al. (Nov. 15 issue)[1] overstate the benefits of anticoagulation. They state that the authors "found no difference between aspirin and warfarin in the prevention of recurrent ischemic stroke or death or in the rate of major hemorrhage. Consequently, [the authors] regard both warfarin and aspirin as reasonable therapeutic alternatives." Mohr et al. do not clearly distinguish between absence of evidence of an effect and evidence of absence of an effect. The primary null hypothesis was that there would be no difference between the treatments (as in an equivalence trial), yet the sample size was calculated according to a 30 percent difference between treatments (as in a nonequivalence trial). Equivalence trials are usually much larger than nonequivalence trials, and we believe that the study was underpowered.

The point estimate of the hazard ratio for the primary end point was 1.13, equivalent to an absolute excess of 21 recurrent ischemic strokes and deaths per 1000 patients treated with warfarin as compared with aspirin (95 percent confidence limits, 13 fewer to 61 more events per 1000 patients treated). Thus, the Warfarin–Aspirin Recurrent Stroke Study (WARSS) does not rule out the possibility of a clinically important disadvantage with warfarin as compared with aspirin. The conclusions in the Discussion section are fair and balanced and are in line with two recent systematic reviews.[2,3] The final sentence reads, "Aspirin, either alone or in combination with some other antiplatelet agents, appears to be a well-justified choice for the prevention of recurrent ischemic stroke." Aspirin is noted to be cheaper than warfarin and easier to administer. However, the conclusions drawn in the Abstract (the only ones many readers will read) are potentially misleading.

STEPHANIE C. LEWIS, PH.D.
PETER A.G. SANDERCOCK, D.M.
University of Edinburgh
Edinburgh EH4 2XU, United Kingdom
steff.lewis@ed.ac.uk

Editor's note: Dr. Sandercock was a member of the WARSS Adjudication Committee.

1. Mohr JP, Thompson JLP, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444-51.
2. Liu M, Counsell C, Sandercock P. Anticoagulants for preventing recurrence following ischaemic stroke or transient ischaemic attack. In: Cochrane database of systematic reviews. Issue 3. Oxford, England: Update Software, 2001 (computer data base).
3. Algra A, De Schryver ELLM, van Gijn J, Kappelle LJ, Koudstaal PJ. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin. In: Cochrane database of systematic reviews. Issue 4. Oxford, England: Update Software, 2001 (computer data base).

To the Editor: The WARSS investigators should be commended for performing a well-organized, multicenter trial in the search for more efficacious drugs than those currently available for secondary prevention after cerebral ischemia of presumed arterial origin. The investigators may be disappointed that low-intensity anticoagulation (target international normalized ratio [INR], 1.4 to 2.8; achieved median, 1.9) tended not to be better than the current touchstone, aspirin (325 mg daily), in reducing the incidence of the primary outcome (ischemic stroke or death from any cause). We were disappointed when high-intensity anticoagulation (target INR, 3.0 to 4.5) turned out to cause major bleeding complications at an unacceptably high rate in the Stroke Prevention in Reversible Ischemia Trial (SPIRIT).[1] Recently, we sought to determine the optimal level of anticoagulation in an observational study of 356 patients similar to those in WARSS and SPIRIT who were referred to the Red Cross Anticoagulation Clinic, Leiden, the Netherlands.[2] During

a two-year follow-up, 19 ischemic and 25 hemorrhagic events occurred. The optimal achieved INR was between 2.5 and 3.5. We therefore think that the interpretation offered by Powers in his editorial — that it is "unlikely" that "oral anticoagulant therapy at some target INR level intermediate between these two levels [those of WARSS and SPIRIT] will be superior to aspirin"[3] — is premature.

ALE ALGRA, M.D.
University Medical Center Utrecht
3508 GA Utrecht, the Netherlands
a.algra@neuro.azu.nl

FOR THE EUROPEAN–AUSTRALIAN STROKE PREVENTION IN REVERSIBLE ISCHEMIA TRIAL STUDY GROUP

1. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. Ann Neurol 1997;42:857-65.
2. Torn M, Algra A, Rosendaal FR. Oral anticoagulation for cerebral ischemia of arterial origin: high initial bleeding risk. Neurology 2001;57:1993-9.
3. Powers WJ. Oral anticoagulant therapy for the prevention of stroke. N Engl J Med 2001;345:1493-5.

To the Editor: Mohr and colleagues address an important clinical issue in their comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. The authors conclude that the efficacy and safety of warfarin and aspirin are similar in patients with inferred noncardioembolic ischemic stroke. However, they do not provide details about the status of the aorta on noninvasive imaging such as transesophageal echocardiography. Amarenco et al.[1] used transesophageal echocardiography in their study of the prevalence of ulcerated aortic plaques in large numbers of patients with stroke. Ulcerated aortic plaques were present in 28 percent of the patients with a brain infarct and in 61 percent of those with no known cause of cerebral infarction. Cohen et al.[2] pointed out that in patients with ischemic stroke, the risk of vascular events associated with an aortic-plaque thickness of 4 mm or more is markedly increased by the absence of plaque calcification. In another study, transesophageal echocardiography identified ulcerated atherosclerotic plaques in the thoracic aorta in 39 percent of patients with unexplained ischemic strokes.[3] The mobility of the protruding plaques may have important therapeutic implications. Vaduganathan et al.[4] compared findings of aortic plaques on transesophageal echocardiography with the results of pathological examination and showed that thrombi were present in all the samples with mobile aortic plaques. Antiplatelet and statin therapy should be advised as a first-line therapy in the majority of patients with stroke.

Transesophageal echocardiography, by identifying mobile aortic plaques, intracardiac thrombi, or certain intracardiac shunts, can help guide the choice of anticoagulation treatment in patients with cryptogenic ischemic stroke.

DAVID H. HSI, M.D.
DARRICK J. ALAIMO, M.D.
Park Ridge Hospital
Rochester, NY 14626
dhsi@hospitals-doctors.com

1. Amarenco P, Duyckaerts C, Tzourio C, Hénin D, Bousser M-G, Hauw J-J. The prevalence of ulcerated plaques in the aortic arch in patients with stroke. N Engl J Med 1992;326:221-5.
2. Cohen A, Tzourio C, Bertrand B, et al. Aortic plaque morphology and vascular events: a follow-up study in patients with ischemic stroke. Circulation 1997;96:3838-41.
3. Stone DA, Hawke MW, LaMonte M, et al. Ulcerated atherosclerotic plaques in the thoracic aorta are associated with cryptogenic stroke: a multiplane transesophageal echocardiographic study. Am Heart J 1995;130:105-8.
4. Vaduganathan P, Ewton A, Nagueh SF, Weilbaecher DG, Safi HJ, Zoghbi WA. Pathologic correlates of aortic plaques, thrombi and mobile "aortic debris" imaged in vivo with transesophageal echocardiography. J Am Coll Cardiol 1997;30:357-63.

To the Editor: The WARSS investigators provide data about five groups defined according to the clinically inferred mechanism of stroke. Among these five groups, there was a group of 576 patients with cryptogenic stroke. In many patients (up to 50 percent) with cryptogenic stroke who are less than 55 years of age, the role of patent foramen ovale in the recurrence of thromboembolic events has been shown.[1,2] It would be interesting to have information about the presence of patent foramen ovale in the patients with cryptogenic stroke in WARSS. In our series of patients with cryptogenic stroke who underwent percutaneous closure of patent foramen ovale and were followed for a median of 15 months (range, 1 to 50), 2 of 86 patients (2.3 percent) had recurrent ischemic stroke.[3] This rate of recurrence is quite low when compared with rates of 15.0 percent and 16.5 percent — the rates in the patients in WARSS who had cryptogenic stroke (those who were given warfarin and those who were given aspirin, respectively).

GIANFRANCO BUTERA, M.D., PH.D.
MASSIMO CHESSA, M.D., PH.D.
MARIO CARMINATI, M.D.
Istituto Policlinico San Donato
20097 San Donato Milanese, Italy
gianfra.but@lycos.com

1. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148-52.
2. Webster MW, Chancellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-2.
3. Butera G, Bini MR, Chessa M, Bedogni F, Onofri M, Carminati M. Transcatheter closure of patent foramen ovale in patients with cryptogenic stroke. Ital Heart J 2001;2:115-8.

The authors reply:

To the Editor: Algra's comments suggest that a test of higher INR ranges than those examined in our study might have shown a greater benefit with warfarin than with aspirin. Apart from our support of Powers's carefully chosen words in his editorial, we cite again concern about safety at this and higher ranges.[1] Nonetheless, we would welcome the results of a randomized, double-blind trial in a sample of adequate size.

We doubt that "many" *Journal* devotees are mere slipshod scanners of abstracts, and we consider the usual reader already clear on the response we offer to Lewis and Sandercock: WARSS was designed as an efficacy trial, not an equivalency trial. It was designed to detect the same 30 percent

difference that had been found in trials that compared warfarin and aspirin for atrial fibrillation, and it was not underpowered. The null hypothesis was not rejected (P=0.25). The overall result (hazard ratio, 1.13; 95 percent confidence interval, 0.92 to 1.38) favored aspirin somewhat, although there was only weak evidence (likelihood ratio, <2) in favor of the hypothesis that there actually is such a benefit, as compared with the hypothesis that there is no difference between aspirin and warfarin. In the Abstract we express our conclusion — that our equipoise remains undisturbed by the result (aspirin and warfarin are "reasonable therapeutic alternatives"). In the Discussion section we acknowledge, however, that "aspirin . . . appears to be a well-justified choice." Both of these interpretations are legitimate, and there is room for debate over the clinical implications of the WARSS data. We did not, however, mistake "absence of evidence" for "evidence of absence." This suggestion requires the ex post facto reinterpretation of WARSS as an equivalency trial, which is not a legitimate approach.

In response to Hsi and Alaimo and to Butera et al.: the Patent Cardiac Foramen Ovale in Cryptogenic Stroke Study (PICSS) is one of several substudies conducted in our cohort.[2] The results of PICSS are currently under review for publication. PICSS may yield insights into the appropriate medical regimen for findings such as aortic-arch atheroma and valvular strands.

J.P. MOHR, M.D.
J.L.P. THOMPSON, PH.D.
B. LEVIN, M.D.
Columbia Presbyterian Medical Center
New York, NY 10032
jpm10@columbia.edu

FOR THE WARFARIN–ASPIRIN RECURRENT STROKE STUDY GROUP

1. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. Stroke 2000;31:817-21.
2. The WARSS, APASS, PICSS, HAS, and GENESIS Study Groups. The feasibility of a collaborative double-blind study using an anticoagulant: the Warfarin–Aspirin Recurrent Stroke Study (WARSS), the Antiphospholipid Antibodies and Stroke Study (APASS), the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), the Hemostasis System Activation Study (HAS), the Genes in Stroke Study (GENESIS). Cerebrovasc Dis 1997;7:100-12.

The editorialist replies:

To the Editor: Algra disagrees with my conclusion that oral anticoagulation at an INR level between those studied in WARSS and SPIRIT[1] is unlikely to be superior to aspirin for the prevention of recurrent noncardioembolic stroke. He cites as evidence a recent study of patients undergoing oral anticoagulation for cerebral ischemia in which an INR between 2.5 and 3.5 was "optimal."[2] This study analyzed the total occurrence of both hemorrhagic and thromboembolic events in these patients. The incidence of thromboembolism was actually lowest at an INR between 3.0 and 3.9, and the risk of hemorrhage was lowest within this INR range as well. It was not a randomized trial, so there was no control group receiving antiplatelet treatment for comparison. Thus, although it can be concluded from this study that an INR between 3.0 and 3.9 may be the optimal level of oral anticoagulation, no conclusion regarding the superiority of this approach over antiplatelet treatment can be made.

On the other hand, both WARSS and SPIRIT[1] are randomized, controlled trials. Neither provides evidence that oral anticoagulation offers a benefit with respect to thromboembolic events. Given the lack of benefit in SPIRIT in the prevention of thromboembolic events with oral anticoagulation at an INR between 3.0 and 4.5, it is difficult to see how reducing the INR to a lower level would provide better protection, even if adverse hemorrhagic events are ignored. However, as I point out in my editorial, the confidence intervals in SPIRIT are too wide to rule out such a benefit. As long as the data are not definitive, it is ethical and proper to conduct a clinical trial such as the European–Australian Stroke Prevention in Reversible Ischemia Trial. In the meantime, extrapolations based on the available data, albeit less than perfect, must be made to guide patient care. It is my conclusion that the best available evidence at this time does not support the use of oral anticoagulation at any INR as a general strategy to prevent recurrent noncardioembolic stroke.

WILLIAM J. POWERS, M.D.
Washington University School of Medicine
St. Louis, MO 63110
wjp@npg.wustl.edu

1. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. Ann Neurol 1997;42:857-65.
2. Torn M, Algra A, Rosendaal FR. Oral anticoagulation for cerebral ischemia of arterial origin: high initial bleeding risk. Neurology 2001;57:1993-9.

Nonsteroidal Drugs and Alzheimer's Disease

To the Editor: The study by in 't Veld et al. (Nov. 22 issue)[1] on the prevention of Alzheimer's disease with nonsteroidal antiinflammatory drugs (NSAIDs) includes no mortality data. It is entirely possible that patients who received long-term treatment with NSAIDs were dying sooner from the complications. One may then underestimate the risk of Alzheimer's disease, giving a false positive result. There are also no data on morbidity. The small group of patients receiving NSAIDs for more than 24 months was the only group with a statistically significant reduction in the risk of Alzheimer's disease. It may be inappropriate to base a positive conclusion on an analysis of only 233 patients.

Although there is some evidence of an effect of NSAIDs, the safety and cost effectiveness of such an intervention are questionable. Gastrointestinal toxicity of NSAIDs alone causes 100,000 to 400,000 hospitalizations every year in the United States, with an estimated yearly cost of $2 billion.[2] Unless we develop a reliable way to predict Alzheimer's disease, it will be hard to justify a randomized, controlled, blinded trial with these potentially toxic medications.

AMIT SOOD, M.D.
Ocean Beach Hospital
Ilwaco, WA 98624
amitricha@pol.net

1. in 't Veld BA, Ruitenberg A, Hofman A, et al. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. N Engl J Med 2001;345:1515-21.
2. Smalley WE, Griffin MR. The risks and costs of upper gastrointestinal disease attributable to NSAIDs. Gastroenterol Clin North Am 1996;25:373-96.

To the Editor: In the report by in 't Veld et al., the investigators used a sophisticated Cox model and found a significantly reduced risk of Alzheimer's disease in patients who had taken NSAIDs for a cumulative period of 24 months or more. We have serious reservations about the main outcome modeled by the Cox regression. The authors "calculated the person-time between January 1, 1991, and death, a diagnosis of dementia, or the end of the study period, whichever came first." However, they provided no information concerning the time of censoring of competing events such as death and a diagnosis of dementia. We understand that the event of interest was dementia and that death was censored. But the statistical model may be misleading, because a patient who has died is no longer at risk for dementia. In addition, if death was due to drug toxicity, it could artificially increase the benefit attributed to NSAIDs. On the other hand, if death was not censored, death and dementia could be considered a composite outcome, but they probably do not share the same prognostic factors. Our suggestion is to use the multistates extension of the Cox model.[1] We used it to explore long-term, treatment-related morbidity in patients with lymphoma and showed that the assumption of the uniformity of prognostic factors or treatment effect on different event rates such as morbidity or mortality was not valid.[2]

NICHOLAS MOUNIER, M.D.
MARC ANDRÉ, M.D.
ERIC LEPAGE, M.D., PH.D.
Centre Hospitalier Universitaire Henri Mondor
94010 Creteil, France
nicolas.mounier@sls.ap-hop-paris.fr

1. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer-Verlag, 2000:350.
2. André MPE, Mounier N, Leleu X, et al. Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma (NHL) with the ACVBP regimen: a GELA (Groupe d'Etude des Lymphomes de l'Adulte) cohort study on 2849 patients. Blood 2001;98:768a. abstract.

To the Editor: In 't Veld et al. report an association between the use of NSAIDs and a reduced incidence of Alzheimer's disease. They suggest that NSAIDs may exert this effect by blockade of cyclooxygenase-1 and cyclooxygenase-2 or by activation of the peroxisome proliferator γ (PPARγ) nuclear transcription factor. However, more than 50 percent of the NSAIDs recorded in their study do not activate PPARγ (e.g., diclofenac), which underlines the importance of the suppression of cerebral prostaglandin production by NSAIDs as a possible mechanism to reduce the risk of Alzheimer's disease.

The authors state that the use of acetaminophen has not been assessed, because acetaminophen is available without a prescription. A previous study found acetaminophen to be protective against Alzheimer's disease.[1] Whereas acetaminophen has only minimal effects on prostaglandin synthesis in monocytes, prostaglandin synthesis is markedly suppressed by acetaminophen in microglia.[2] Therefore, reduction of cerebral prostaglandin production may have an even greater effect on Alzheimer's disease than the effect reported by the authors, since patients using acetaminophen may have been included in the group of subjects without prescriptions for NSAIDs.

MICHAEL HÜLL, M.D.
KLAUS LIEB, M.D.
BERND L. FIEBICH, PH.D.
University of Freiburg Medical School
D-79104 Freiburg, Germany
michael_huell@psyallg.ukl.uni-freiburg.de

1. Breitner JC, Welsh KA, Helms MJ, et al. Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs. Neurobiol Aging 1995;16:523-30.
2. Fiebich BL, Lieb K, Hüll M, et al. Effects of caffeine and paracetamol alone or in combination with acetylsalicylic acid on prostaglandin E(2) synthesis in rat microglial cells. Neuropharmacology 2000;39:2205-13.

To the Editor: In 't Veld et al. found that those taking NSAIDs had a lower risk of Alzheimer's disease. The prevailing view has been that this effect occurs through inhibition of cyclooxygenase, reducing the inflammation associated with Alzheimer's disease.[1] Weggen et al. recently found that certain NSAIDs lower the amount of amyloidogenic 42-residue β-amyloid (Aβ42) protein independently of their effects on cyclooxygenase.[2] Although the effect was found at clinically relevant concentrations for ibuprofen, sulindac, and indomethacin, it was not found for naproxen. Given the large number of patients taking either ibuprofen or naproxen in the study by in 't Veld et al., it would be helpful to know whether the relative risk of Alzheimer's disease differed between these two groups.

DANIEL PRESS, M.D.
Beth Israel Deaconess Medical Center
Boston, MA 02215
dpress@caregroup.harvard.edu

1. Rogers J, Webster S, Lue LF, et al. Inflammation and Alzheimer's disease pathogenesis. Neurobiol Aging 1996;17:681-6.
2. Weggen S, Eriksen JL, Das P, et al. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. Nature 2001;414:212-6.

The authors reply:

To the Editor: Both Sood and Mounier et al. point out that no mortality data were provided in our report on NSAIDs and the risk of Alzheimer's disease. They suggest that a protective effect of NSAIDs might be explained by increased mortality. We considered this possibility, but we found no association between the use of NSAIDs and mortality in the remaining 6595 elderly patients without dementia. Hence, increased mortality in our users of NSAIDs without dementia does not appear to explain our results. The risk of death from any cause was 1.07 (95 percent confidence interval, 0.82 to 1.40) in patients who had used NSAIDs for two years or more and 0.97 (95 percent confidence interval, 0.86 to 1.08) in those who had used NSAIDs for less than

two years, as compared with patients who did not use NSAIDs. We disagree with Sood that a positive conclusion cannot be based on 233 patients, as long as the data are cautiously interpreted. We agree, however, that the risk of gastrointestinal toxicity is high and that the cost effectiveness of the use of NSAIDs as a therapeutic intervention would require careful study. The suggestion by Hüll et al., who studied the effect of acetaminophen on microglial effects in rats,[1] is interesting. A problem is that acetaminophen is widely available over the counter in the Netherlands and misclassification of exposure may be substantial. Press refers to a study published shortly before ours that suggested that some NSAIDs (e.g., ibuprofen) may protect against Alzheimer's disease by lowering levels of amyloidogenic Aβ42 peptide, whereas other NSAIDs (e.g., naproxen) have no such effect.[2] Although ibuprofen and naproxen were among the most commonly used NSAIDs in our study, the numbers were too low to justify a comparison between individual agents.

BRUNO H.C. STRICKER, M.D., PH.D.
ALBERT HOFMAN, M.D., PH.D.
MONIQUE M.B. BRETELER, M.D., PH.D.
Erasmus Medical Center
3000 DR Rotterdam, the Netherlands

1. Fiebich BL, Lieb K, Hüll M, et al. Effects of caffeine and paracetamol alone or in combination with acetylsalicylic acid on prostaglandin E(2) synthesis in rat microglial cells. Neuropharmacology 2000;39:2205-13.
2. Weggen S, Eriksen JL, Das P, et al. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. Nature 2001;414:212-6.

Valsartan in Chronic Heart Failure

To the Editor: Cohn and Tognoni (Dec. 6 issue)[1] found that the angiotensin-receptor blocker valsartan reduced the combined end point of mortality and morbidity and improved clinical signs and symptoms in patients with heart failure when it was added to prescribed therapy. However, an adverse effect on mortality and morbidity was observed in a subgroup receiving valsartan, an angiotensin-converting–enzyme (ACE) inhibitor, and a beta-blocker. In the overall study, adverse events leading to the discontinuation of valsartan included dizziness, hypotension, and renal impairment, but hypotension was not significantly more frequent in the valsartan group than in the placebo group. The authors state that "extensive blockade of multiple neurohumoral systems in patients with heart failure could be deleterious." Clinicians should keep this possibility in mind when they are considering the use of vasodilator therapy, since hypotension reduces perfusion pressure to the brain and heart, resulting in cerebral and myocardial damage. Was there a significant incidence of hypotension and cerebral and myocardial damage in the subgroup, which led to an increase in mortality?

FRANCIS J. HADDY, M.D., PH.D.
211 Second St. NW, 1607
Rochester, MN 55901-2896
tbhaddy@aol.com

Editor's note: Dr. Haddy holds stock in Novartis.

1. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.

To the Editor: Cohn and Tognoni report that the addition of valsartan to standard therapy for heart failure reduced the combined end point of mortality and morbidity in all patients except those who were receiving both an ACE inhibitor and a beta-blocker at base line; in this subgroup, mortality was significantly increased. The authors acknowledge that extensive blockade of multiple neurohormonal systems in patients with heart failure could be deleterious.

My colleagues and I recently reported that beta-blockade reduces angiotensin II levels in patients with heart failure who are receiving ACE inhibitors.[1] Our findings are consistent with the well-described ability of beta-blockade to reduce renin secretion.[2] Thus, the combination of ACE inhibition, beta-blockade, and angiotensin-receptor blockade represents triple inhibition of the renin–angiotensin system. Studies in animals indicate that extensive blockade of the renin–angiotensin system has deleterious effects, particularly in the presence of sodium depletion.[3,4] Whereas single or double blockade of the renin–angiotensin system (with the use of either ACE inhibition and beta-blockade or ACE inhibition and angiotensin-receptor blockade) is beneficial in patients with heart failure, triple blockade may be deleterious. The risk of harm may be increased by sodium depletion resulting from diuretic therapy. Measurement of angiotensin II levels may provide a means to identify patients who have little to gain — and who may be harmed — by the addition of an angiotensin-receptor blocker to their heart-failure regimen.

DUNCAN JOHN CAMPBELL, M.D., PH.D.
St. Vincent's Institute of Medical Research
Fitzroy, VIC 3065, Australia
j.campbell@medicine.unimelb.edu.au

Editor's note: Dr. Campbell has a research contract with Solvay Pharmaceutical.

1. Campbell DJ, Aggarwal A, Esler M, Kaye D. β-Blockers, angiotensin II, and ACE inhibitors in patients with heart failure. Lancet 2001;358:1609-10.
2. Bühler FR, Laragh JH, Baer L, Vaughan ED Jr, Brunner HR. Propranolol inhibition of renin secretion: a specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. N Engl J Med 1972;287:1209-14.
3. Ménard J, Campbell DJ, Azizi M, Gonzales MF. Synergistic effects of ACE inhibition and Ang II antagonism on blood pressure, cardiac weight, and renin in spontaneously hypertensive rats. Circulation 1997;96:3072-8.
4. Griffiths CD, Morgan TO, Delbridge LM. Effects of combined administration of ACE inhibitor and angiotensin II receptor antagonist are prevented by a high NaCl intake. J Hypertens 2001;19:2087-95.

To the Editor: There are two problems with the conclusion of Cohn and Tognoni that valsartan improves outcomes in patients with chronic heart failure. First, since the average dose of standard therapy with ACE inhibitors in the base-line population was quite low, it is not logical to conclude that the benefits noted in the valsartan group were due to valsartan. It has been well demonstrated that ACE inhibitors are frequently underused in patients with heart failure and that the doses prescribed are too small.[1] Furthermore, a 1999 study demonstrated that 30 mg of lisinopril daily was supe-

rior to a daily dose of 5 to 10 mg in reducing the risk of death and hospitalization,[2] yet the average dose of lisinopril in the current study was only 19 mg daily. Until valsartan is evaluated in a study of patients with heart failure in which appropriately therapeutic doses of ACE inhibitors are used, it remains in question whether the benefits noted are specific to valsartan or would be equal or inferior to those obtained with higher doses of ACE inhibitors.

Second, and of more concern, is the post hoc finding that the addition of valsartan to a regimen of an ACE inhibitor and a beta-blocker significantly increased the risk of death and nonsignificantly increased the risk of the combined end point of mortality and morbidity. Among patients who were already receiving appropriate treatment, the outcome was better if placebo was given than if valsartan was given.

WILLIAM E. CAYLEY, JR., M.D.
Eau Claire Family Medicine
Eau Claire, WI 54701
bcayley@yahoo.com

1. Bungard TJ, McAlister FA, Johnson JA, Tsuyuki RT. Underutilisation of ACE inhibitors in patients with congestive heart failure. Drugs 2001;61:2021-33.
2. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999;100:2312-8.

To the Editor: The results reported by Cohn and Tognoni indicate a lack of effect of valsartan on mortality in the population studied but a small reduction in the rate of a first adverse event. Although the results of subgroup analyses should be treated with great caution, differences in mortality are noteworthy. We were therefore surprised that the significant increase in mortality with valsartan therapy, as compared with placebo, in the subgroup that was receiving both beta-blockers and ACE inhibitors (mortality rates, 16.2 percent and 11.9 percent, respectively) was presented only in the form of a relative risk and received only brief mention. It is difficult to understand why an absolute difference in mortality of 4.3 percent, meaning that 1 extra death occurred for every 23 patients in this subgroup who received valsartan, is worthy of such little comment and presented only in terms of relative risk. We believe that this result is by far the most important finding of the subgroup analyses and must be a cause for concern, given the current trend in many clinical trials involving patients with heart failure to use combination therapy to disable the renin–angiotensin–aldosterone–sympathetic nervous system.

J. COLIN FORFAR, M.D., PH.D.
SHAHZAD MUNIR, M.B., CH.B.
John Radcliffe Hospital
Oxford OX3 9DU, United Kingdom
colin.forfar@orh.nhs.uk

The authors reply:

To the Editor: The issue of the possible adverse effect of combined therapy with an ACE inhibitor, a beta-blocker, and an angiotensin-receptor blocker, mentioned by Drs. Haddy and Campbell, is one that has concerned us as well. Valsartan lowered blood pressure to a similar degree in all subgroups, although the group treated with an ACE inhibitor and a beta-blocker had a slightly lower blood pressure at base line. We did not find a greater incidence of symptoms of hypotension or end-organ damage in this subgroup.

Dr. Campbell's reaffirmation of the renin-inhibiting effect of beta-blockers provides an attractive hypothesis that potent renin–angiotensin blockade is the culprit, but the physiological mechanism of this as yet unconfirmed adverse effect remains unclear. The results of other ongoing clinical trials in which large numbers of patients are receiving the three-drug combination for various cardiovascular diseases may help to determine whether the interaction is real.

Dr. Cayley and Drs. Forfar and Munir question our interpretation of the results of the trial. Although the average dose of ACE inhibitors prescribed to our patients was remarkably close to the doses used in previous clinical trials and not "quite low," as characterized by Dr. Cayley, we agree that higher doses might have provided greater benefit. We disagree, however, with his characterization of an appropriate dose of an ACE inhibitor. Successful trials have targeted the equivalent of 20 mg of lisinopril daily, and the 1999 trial to which he referred unfortunately provided no evidence that a 30-mg dose is better than a 20-mg dose.[1] We have not suggested that the efficacy of valsartan is unique, but the efficacy of higher doses of an ACE inhibitor has not been evaluated in this context.

We emphasized in the article the potential adverse effect of high-dose valsartan in patients who were already receiving an ACE inhibitor and a beta-blocker, but we must stress again the danger of placing too much confidence in the results of a post hoc subgroup analysis. The adverse effect on mortality of the triple-inhibitor regimen certainly warrants our attention, but the overall design and the protocol-driven results of the trial — a 13.2 percent reduction in the combined end point of mortality and morbidity — must take precedence.[2]

JAY N. COHN, M.D.
University of Minnesota Medical School
Minneapolis, MN 55455
cohnx001@umn.edu

GIANNI TOGNONI, M.D.
Istituto di Ricerche Farmacologiche Mario Negri
20157 Milan, Italy

1. Nicklas JM, Cohn JN, Pitt B. What does ATLAS really tell us about "high" dose angiotensin-converting enzyme inhibition in heart failure? J Card Fail 2000;6:165-8.
2. Wedel H, Demets D, Deedwania P, et al. Challenges of subgroup analyses in multinational clinical trials: experiences from the MERIT-HF trial. Am Heart J 2001;142:502-11.

Botulinum Toxin for Cricopharyngeal Dysfunction in Parkinson's Disease

To the Editor: Dysphagia occurs in more than 50 percent of patients with Parkinson's disease.[1] Although all the phas-

es of swallowing can be involved, dysphagia due to hyperactivity of the upper esophageal sphincter is the prevalent abnormality.[1]

Dysphagia does not respond to dopaminergic therapy.[1] Surgical myotomy of the cricopharyngeal muscle is the treatment of choice for hyperactivity of the upper esophageal sphincter due to neurologic disorders,[2] including Parkinson's disease.[3] However, cricopharyngeal myotomy requires general anesthesia and is not always effective.[2]

Botulinum neurotoxin type A has been used to treat dysphagia.[4,5] We describe its use in four patients (three men and one woman; age range, 58 to 72 years) with Parkinson's disease and dysphagia. In these patients, dysphagia for solid food had progressed to dysphagia for liquids, and the diet had become confined to semiliquid meals. The mean duration of dysphagia was 5.9 years.

All the patients were receiving levodopa and decarboxylase inhibitors, but there was no improvement of the dysphagia. Videofluoroscopic studies showed a reduction of pharyngeal clearance and incomplete cricopharyngeal opening. Electromyographic studies of both the cricopharyngeal and the pharyngeal inferior constrictor muscles showed abnormal tonic hyperactivity of the former.

To evaluate the possible efficacy of cricopharyngeal myotomy, we decided to treat the cricopharyngeal muscle with botulinum neurotoxin type A. After the patients had given written informed consent and the local ethics committee had approved the treatment, both cricopharyngeal muscles were percutaneously injected with botulinum neurotoxin type A (Dysport, Ipsen, Wrexham, United Kingdom; 30 units per muscle) under electromyographic control. Forty-eight hours later, all patients had remarkable improvement in swallowing. Clinical, electromyographic, and videofluoroscopic examinations were performed 8, 16, 20, and 22 weeks after the injection. At eight weeks, all the patients were able to swallow. Videofluoroscopic and electromyographic studies showed normal swallowing and coordination between the cricopharyngeal and inferior constrictor muscles and a marked reduction in cricopharyngeal hyperactivity. The improvement persisted at 16 and 20 weeks in all four patients and disappeared in three of them at 22 weeks. All patients gained 5 to 8 kg in body weight.

Given its safety and effectiveness, we propose that treatment with botulinum neurotoxin type A may be a successful alternative to invasive procedures or may be a useful tool for identifying patients who might benefit from surgical myotomy.

DOMENICO A. RESTIVO, M.D., PH.D.
AGOSTINO PALMERI, M.D., PH.D.
University of Catania
95125 Catania, Italy
darestivo@eudoramail.com

ROSARIO MARCHESE-RAGONA, M.D.
University of Padua
35100 Padua, Italy

1. Hunter PC, Crameri J, Austin S, Woodward MC, Hughes AJ. Response of parkinsonian swallowing dysfunction to dopaminergic stimulation. J Neurol Neurosurg Psychiatry 1997;63:579-83.
2. McKenna JA, Dedo HH. Cricopharyngeal myotomy: indications and technique. Ann Otol Rhinol Laryngol 1992;101:216-21.
3. Born LJ, Harned RH, Rikkers LF, Pfeiffer RF, Quigley EM. Cricopharyngeal dysfunction in Parkinson's disease: role in dysphagia and response to myotomy. Mov Disord 1996;11:53-8.
4. Schneider I, Thumfart WF, Pototschnig C, Eckel HE. Treatment of dysfunction of the cricopharyngeal muscle with botulinum A toxin: introduction of a new, noninvasive method. Ann Otol Rhinol Laryngol 1994;103:31-5.
5. Restivo DA, Marchese Ragona R, Staffieri A, de Grandis D. Successful botulinum toxin treatment of dysphagia in oculopharyngeal muscular dystrophy. Gastroenterology 2000;119:1416.

Large Errors in the Dosing of Medications for Children

To the Editor: Dosing errors are among the most common types of medication errors.[1-3] Errors by a factor of 10 (the administration of a dose 10 times or 1/10 as high as appropriate) are of particular concern.[4] There is a greater chance that an infant or a young child will receive such a dose of medication than that an adult will, because even a dose 10 times as high as the appropriate pediatric dose may represent an unsuspiciously small volume of stock solution.

We reviewed all forms of errors involving medication that were reported to the pharmacy department at a large tertiary care pediatric hospital between April 1 and November 1, 2000. The hospital has a unit-dose system for dispensing drugs and a computerized system for prescribing medications. Twenty errors by a factor of 10 were spontaneously reported (1 per 22,500 doses). The errors involved 19 different medications. Most of these errors involved pharmacologically potent drugs, so that such an error could potentially result in death (in six cases), life-threatening toxic effects (in nine cases), or moderate toxic effects (in one case); in the remaining four cases, the error could not have resulted in toxic effects. Since many of the drugs are highly potent, they are usually given in doses of less than 1 mg per kilogram of body weight, creating a potential source of confusion during the conversion of milligrams to micrograms (Table 1). Most of the drugs were not among the 20 most commonly used medications in our hospital. Of the 20 incorrect doses,

TABLE 1. MEDICATIONS INVOLVED IN LARGE DOSING ERRORS.

DRUGS WITH A RECOMMENDED DOSE GIVEN IN UNITS	DRUGS WITH A RECOMMENDED INITIAL DOSE OF <1 mg/kg IN CHILDREN	DRUGS WITH A RECOMMENDED INITIAL DOSE OF ≥1 mg/kg IN CHILDREN
Heparin*	Amphotericin B	Ampicillin
Penicillin G	Captopril	Cefazolin
	Clonidine	Cefuroxime
	Digoxin	Diazoxide
	Epinephrine	Gentamicin
	Milrinone	Indomethacin
	Morphine	Meperidine
	Pancuronium	Cyclosporine
	Albuterol	

*Two dosing errors involved heparin.

5 reached the children (one newborn, one child 1.5 years of age, one 3.5 years of age, one 8 years of age, and one 12 years of age) and 15 were intercepted. Physicians were responsible for 18 of the 20 errors.

To estimate the proportion of these large dosing errors that are reported spontaneously, we compared the rate of spontaneous reports from the emergency department with the rate of those found through audits of the charts in the emergency department for 12 randomly selected days. Two such errors were reported spontaneously by the emergency department (incidence, 1 per 13,000; 95 percent confidence interval, 0 to 3 per 10,000). The audits found 2 errors among 1532 charts (incidence, 1 per 766; 95 percent confidence interval, 13 to 47 per 10,000; $P=0.005$ for the comparison between the two methods of finding errors). The two errors found during the audits were not reported through the system for the spontaneous reporting of incidents. These findings suggest that spontaneous reports of large dosing errors in children may underestimate the true incidence.

The best strategy for reducing the incidence of large errors in dosing may be to improve the system by which drugs are given. Examples of such approaches are the use of a unit-dose system for dispensing drugs and the use of a computerized system for prescribing medications. However, most of the errors we found occurred despite the use of both of these types of systems, suggesting that the systems have limitations.

ERAN KOZER, M.D.
DENNIS SCOLNIK, M.B., CH.B.
TARA KEAYS, B.SC.H.
KEVIN SHI, B.SC.
TRACY LUK
GIDEON KOREN, M.D.
Hospital for Sick Children
Toronto, ON M5G 1X8, Canada

1. Lesar TS, Lomaestro BM, Pohl H. Medication-prescribing errors in a teaching hospital: a 9-year experience. Arch Intern Med 1997;157:1569-76.
2. Lesar TS. Errors in the use of medication dosage equations. Arch Pediatr Adolesc Med 1998;152:340-4.
3. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse events in pediatric inpatients. JAMA 2001;285:2114-20.
4. Koren G, Barzilay Z, Greenwald M. Tenfold errors in administration of drug doses: a neglected iatrogenic disease in pediatrics. Pediatrics 1986;77:848-9.