AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

Providing the Highest Quality Clinical Information for 18 Years

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

FDA Ruling on Mitoxantrone for Multiple Sclerosis

ABSTRACT & COMMENTARY

Source: Letter from the FDA, January 28, 2000.

On january 28, 2000, an fda advisory panel recommended the approval of mitoxantrone (Novantrone, Immunex Corp.) for progressive forms of multiple sclerosis (MS). The panel had reviewed data presented at meetings, but not yet published in full, of a phase III European trial comparing efficacy of two doses of mitoxantrone (5 and 12 mg/m^2) to placebo in 188 patients with secondary progressive MS. The patient inclusion criteria required progression of at least 1 EDSS over the previous 18 months, with a baseline EDSS between 3 and 6.

Patients receiving mitoxantrone IV every three months for two years had significant improvement in EDSS and ambulation index. The annual relapse rate and time to first relapse also improved. The effect was more pronounced in the higher dose group. In addition, brain MRI evaluations in 110 patients at the high dose showed a significant ($P < 0.05$) reduction in new or enhancing lesions compared to placebo.

Common side effects included alopecia, nausea, urinary tract infections, and leukopenia, but reportedly no substantial cardiotoxicity occurred in this short-term use. Cardiotoxicity, unfortunately, is a well-recognized, cumulative dose-dependent effect of this potent drug in its standard use in acute nonlymphocytic leukemia, so additional long-term safety testing is required. Mitoxantrone may only provide short-term control of MS disease activity, and extended use of the drug will not be possible.

COMMENTARY

Mitoxantrone, therefore, is not likely to be a first-line therapy, but may be an option for patients for severe refractory disease that has not responded to conventional therapy such as interferon-beta. It is unclear if mitoxantrone can be used in combination with, or in sequence with, other approved MS drugs. Hopefully, with improved selective immunomodulatory therapies now in development (e.g., interleukin-12 antagonists), there will be less need for toxic immunosuppressive drug regimens. We await the full publication of the clinical data and a more complete assessment of long-term risks. Concurrent in time with the

Volume 18 • Number 7 • March 2000 • Pages 49-56

INSIDE

above FDA report, Biogen, Inc., on January 31, 2000, released via the public press and National Multiple Sclerosis Society that an independent data and safety monitoring committee determined that Avonex provided a statistically significant delay of onset of clinically definite MS compared with placebo. **—bra**

Gastrostomy in Terminal Dementia?

ABSTRACT & COMMENTARY

Source: Gillick MR. Rethinking the role of tube feeding in patients with advanced dementia. *N Engl J Med* 2000; 342:206-210.

Gillick from the hebrew rehabilitation center for the Aged in Boston challenges the status quo with her title. She estimates that percutaneous endoscopic gastrostomy tubes have been inserted in at least 35,000 overwhelmingly demented patients in the United States during a recent year. Presumably this and other such approaches to hopelessly demented patients that they have no choice but to reach a permanent vegetative state. Furthermore, she accurately and compassionately points out that nasally inserted tube feeding inevitably draws complications that void possible help for the patient. Her editorial emphasizes the complex and painful experience of upper endoscopy, intravenous sedation, and ultimate incision of the abdominal wall. Actually, her empathetic approach to the problem indicates that gastrostomy produces far more irritation than it does to soothe the patient's long-lost capacity to perceive suffering by his/her once-conscious brain. Supporting this concept, Gillick points to a survey that stated via a questionnaire, "among 421 randomly selected, competent patients who were living in 49 nursing homes, only one-third would favor a feeding tube if they were unable to eat because of permanent brain damage."

Neurologists know more about the brain, its wonderful scientific accomplishments, and, unfortunately, its converse potential for disintegration and permanent loss of consciousness at the end of life. Surgeons may have skillful hands and general practitioners may know about functioning visceral organs, but, as a specialty, neurologists know all too well that when a degenerating or overwhelmingly injured brain has lost its capacity for awareness, there is no turning back. Even the American Supreme Court has accepted the principle that nutrition is not a constitutional requirement for patients experiencing total loss of awareness.

COMMENTARY

Alert shares Gillick's beliefs that scientifically and ethically prepared neurologists must assist medical professionals and other caregivers to recognize that severely worsening dementia is terminal and no therapy will turn back the inevitability of death. The sad part of this is that, for whatever reason, many professionals remain resistant to biologically consistent examples that pass before them. **—fp**

Stroke Risks with Carotid Stenosis

ABSTRACTS & COMMENTARY

Sources: Henderson RD, et al. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid stenosis. *Stroke* 2000;31:128-132; Demchuk AM, et al. Specific transcranial Doppler flow findings related to the presence and site of arterial occlusion. *Stroke* 2000;31:140-146.

The nascet1 and ecst2 trials both demonstrated that the risk of stroke in symptomatic patients

Neurology Alert, ISSN 0741-4234, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/ GROUP PUBLISHER: Donald R. Johnston.
EXECUTIVE EDITOR: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
ASSOCIATE MANAGING EDITOR: Robin Mason.
COPY EDITOR: Neill Larmore.

GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $35. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail Address: customerservice@ahcpub.com
Editorial E-Mail Address: neill.larmore@medec.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$209 per year (Student/Resident rate: $105).
Multiple Copies
1-9 additional copies: $188. 10 or more copies: $167.
Canada
Add GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 20 hours of Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

Questions & Comments

Please call **Robin Mason**, Associate Managing Editor, at (404) 262-5517 or **Neill Larmore**, Copy Editor, at (404) 262-5480 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

American Health Consultants does not receive material commercial support for any of its continuing medical education publications. In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Apatoff serves on the speaker's bureau of Biogen and Teva. Dr. Relkin serves on the speaker's bureau of Pfizer, Eisai, and Athena Diagnostics and does research for Pfizer and Merck. Dr. Rubin serves on the speaker's bureau of Athena and does research for Asta Medica. Dr. Plum, Dr. Frucht, Dr. Caronna, and Dr. Segal report no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.

increased with enlarging degrees of internal carotid artery (ICA) stenosis. In the present report, the NASCET group assessed the effect of collaterals on the risk of stroke and TIA in the presence of severe ICA stenosis. Henderson and colleagues determined angiographic collateral filling through anterior communicating (ACoA) and posterior communicating (PCoA) arteries as well as retrograde filling through ophthalmic arteries (OA) in 339 medically treated and 342 surgically treated patients entered into the NASCET study.

The percentage of patients with collaterals increased with the degree of ICA stenosis from 0.5% at less than 50% stenosis to 64% at the highest degree of stenosis ($P < 0.001$). In medically treated patients with severe ICA stenosis, the two-year risk of hemispheric stroke was reduced in the presence of collaterals: 28% to 11% ($P = 0.005$). A similar reduction was observed for hemispheric TIA (36% vs 19%; $P = 0.008$). In surgically treated patients, the reductions of preoperative risk and of the two-year stroke risks were not significant.

The results of this study suggest that collateral circulation is important in reducing the risk of hemisphere stroke and TIA in patients with symptomatic severe ICA stenosis. The reduction in stroke risk was demonstrated when the presence of collaterals was defined as the angiographic visualization of one or more collateral pathways via AcoA, PcoA, or OA. Leptomeningeal collaterals over the hemispheres were not considered for technical reasons. In this study, the AcoA was the most important collateral pathway.

Demchuk and associates evaluated the frequency of specific transcranial Doppler (TCD) flow findings in patients with angiographically proved arterial occlusion. A standard TCD insonation was performed and TCD was interpreted independently of angiographic results. Angiographic occlusion was demonstrated in 48 patients. There were 17 proximal ICA occlusions, 13 distal ICA occlusions, 17 middle cerebral artery (PCA) occlusions, nine distal vertebral artery (VA) occlusions, and five basilar artery (BA) occlusions. The TDC findings in the 17 patients with proximal ICA occlusion are representative. MCA wave forms were abnormal in 67%, flow was reversed in OA in 71%, there was cross-filling via the ACoA in 79%, and PCoA in 71%. There was a contralateral compensatory velocity increase in 85%. Only one of 17 patients with proximal ICA occlusion had no abnormal TCD findings.

COMMENTARY

Assessing collateral pathways may be useful in identifying patients with severe ICA stenosis who are at a lower risk of stroke and TIA and therefore may be spared carotid endarterectomy. Nevertheless, clinicians are unlikely to recommend invasive assessment with transfemoral angiography to patients already possessing severe ICA stenosis already identified by duplex Doppler and magnetic resonance angiography. In this setting, TCD appears to be a method that can be clinically important to identify compensatory flow increases in the ACoA, PcoA, and OA.

In the present study, Demchuk et al found that proximal ICA occlusion commonly produced abnormal wave forms at the ICA siphon but its effect on the ipsilateral MCA wave form depended on the amount of collateral blood flow. TCA reliably detected reversed flow in the OA and both communicating arteries. TCD offers a noninvasive alternative to transfemoral angiography in assessing underlying stroke risks, as well as developing treatment options for prognosis and secondary stroke prevention. **—jjc**

Neurophysiological Alerts

EMG in Syringomyelia

Source: Nogues MA, Stalberg E. Electrodiagnostic findings in syringomyelia. *Muscle Nerve* 1999;22:1653-1659.

The electrodiagnostic distinction of syrinx from motor neuron disease may be impossible. Fibrillation potentials in atrophic arm muscles with sparing of leg muscles is more likely in the former, but both demonstrate normal sensory nerve conduction studies, depressed motor amplitudes, and normal motor conduction velocities. Using multichannel surface EMG recording, as well as routine needle EMG, unique forms of spontaneous activity may be documented in syringomyelia. Among 43 such patients, 10 showed irregular, but continuous, synchronous firing of motor unit potentials in antagonistic muscles, involving finger flexors and extensors ($n = 8$) or the tibialis anterior and gastrocnemius ($n = 2$). Five demonstrated respiratory synkinesis ("breathing arm"), with bursts of motor unit activity in one or more arm muscles synchronous with respiration. In three, muscle contraction was visible though none of the patients was aware of any movement. Continuous motor unit activity, most commonly in finger flexors, invariably in weak, wasted muscles, was found in 18, and myokymic discharges were seen in four, in limb ($n = 3$) or paraspinal muscles ($n = 1$). Fourteen (33%) showed long latency responses on routine nerve conduction studies, recording from the median nerve/abductor pol-

licis brevis (mean latency 97.0 ± 34.6 ms) or tibial nerve/abductor hallucis (mean latency 113.3 ± 47.4 ms). Injury and isolation of the lower motor neuron or inhibitory interneuron, and involvement of the descending spinal pathways, including the vestibulospinal, reticulospinal, and rubrospinal tracts, may underlie these phenomena. **—mr**

EMG in Myositis

Source: Lyu RK, et al. Incidence of irritable electromyography in inflammatory myopathy. *J Clin Neuromusc Dis* 1999; 1:64-67.

Needle electromyographic (emg) examination of myositis nearly always reveals a triad of findings, comprising positive waves, complex repetitive discharges, and myopathic motor unit potentials.[1] However, these abnormalities may not be as sensitive as previously thought. Among 178 consecutive, biopsy-proven cases of myopathy comprising 80 men and 98 women, 47 (26%) and 131 (74%) had inflammatory and noninflammatory histology, respectively, based on the presence or absence of inflammatory cells in the region of necrotic muscle cells, in the presence of type 2 fiber atrophy. Only 31 (66%) of inflammatory, and 39 (30%) of noninflammatory cases demonstrated spontaneous activity (positive waves, fibrillation potentials, or complex repetitive discharges). Interestingly, among the 10 patients with complex repetitive discharges alone, without positive waves or fibrillation potentials, none had inflammatory histology, indicating its lack of predictability in isolation. Overall, spontaneous activity predicted inflammation in only 44%, and was thus neither sensitive nor specific for myositis. **—mr**

EMG in Tomaculous Neuropathy

Source: Andersson PB, et al. Electrodiagnostic features of hereditary neuropathy with liability to pressure palsies. *Neurology* 2000;54:40-44.

Nine patients with hereditary neuropathy with liability to pressure palsies (HNPP, tomaculous neuropathy) were electrodiagnostically compared to 22 patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and 49 patients with diabetic polyneuropathy to determine which nerve conduction features should raise suspicion of HNPP and distinguish it from the latter, with which it is most likely to be confused. Sensory nerve conduction velocities (NCVs) were slowed in 93% of HNPP nerves (27 of 29 tested) with prolonged distal F wave and motor latencies in 90% (18 of 21) and 78% (25 of 32), respectively. Motor NCVs were slowed in only 31% of nerves studied (10 of 32), less frequently than either CIDP (69%) or diabetes (40%). By analysis of variance, mean distal latency prolongation and sensory NCV slowing in HNPP were significant compared to CIDP and diabetic polyneuropathy, and indicate that an underlying, distally predominant, demyelinating polyneuropathy is present in HNPP, quite apart from the focal entrapment neuropathies for which it is renowned. **—mr**

Reference

1. Kimura J. *Electrodiagnosis in Diseases of Nerve and Muscle.* 2nd ed. Philadelphia, PA: FA Davis Co.; 1989.

EMG in X-Linked CMT

Source: Gutierrez A, et al. Unusual electrophysiological findings in X-linked dominant Charcot-Marie-Tooth disease. *Muscle Nerve* 2000;23:182-188.

X-linked dominant charcot-marie-tooth disease (CMTX) is the second most common form of CMT and the result of a connexin 32, gap-junction protein gene mutation. Variable and intermediate range velocity slowing has raised uncertainty as to whether this is due to large fiber axonal dropout or primary demyelination. Nerve conduction studies of five genetically confirmed CMTX patients revealed decreased compound muscle action potentials (CMAP), prolonged F wave latencies, and, surprisingly, nonuniform conduction velocities between and within nerves, as demonstrated by differential slowing along a nerve, and temporal dispersion (> 40% increased duration of CMAP proximally compared to distally). These demyelinating features, confirmed by sural nerve biopsy, which revealed uniform loss of myelinated fibers and onion bulbs in the absence of inflammation, indicate that this hereditary neuropathy is demyelinating in nature but has the unique characteristics of acquired disease of temporal dispersion and nonuniform slowing. **—mr**

Genetic Link Found in Recurrent Lobar Intracerebral Hemorrhage

ABSTRACT & COMMENTARY

Source: O'Donnell HC, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. *N Engl J Med* 2000;342:240-245.

Cerebral amyloid angiopathy (caa) is characterized by abnormal deposition of amyloid protein in cortical and leptomeningeal blood vessels. CAA is frequently associated with lobar intracerebral hemorrhage. Previous studies have shown a link between the occurrence of CAA and possession of either the e2 or e4 allele of apolipoprotein E (APOE). The results of a new prospective cohort study by O'Donnell and colleagues from the Massachusetts General Hospital and Spaulding Rehabilitation Hospital in Boston indicate that the APOE genotype may be useful for identifying patients at increased risk for recurrence of intracerebral bleeding after an episode of lobar hemorrhage attributable to CAA.

The finding is based on the study of 71 patients with a mean age of 75 years who had suffered at least one lobar intraparenchymal bleed and consented to undergo genetic testing and longitudinal follow-up for two years. Ten members of the cohort subsequently died and underwent a postmortem examination that confirmed the presence of definite CAA. An additional 39 subjects were thought to have probable CAA on the basis of radiographic evidence of multiple small lobar hemorrhages. The remaining 22 were found to have had only one hemorrhagic event and were accordingly deemed to have possible CAA. During the two-year follow-up period, a total of 19 patients in this cohort had recurrent symptomatic hemorrhages, eight of whom died.

As in previous studies of patients, both the APOE e2 and e4 alleles were found to be over-represented among the study participants with CAA. Among several variables examined (including age, gender, the presence of hypertension, diabetes, and dementia), the only significant predictors of recurrence were a prior history of hemorrhagic stroke and APOE genotype. The two-year recurrence rate among carriers of APOE e2 and e4 was 28%, compared to 10% among those with APOE e3. Time to recurrence was least in those with the e2/e4 genotype, with four of eight patients in this group having recurrence of lobar hemorrhage within the first six months of follow-up. Previous hemorrhagic stroke was associated with more than sixfold increased risk of recurrence (risk ratio = 6.4, 95% CI = 2.2-18.5). The risk ratios for recurrence with possession of e2 and e4 were 4.7 (95% CI = 1.4-15.9) and 3.7 (95% CI = 1.1-11.7), respectively.

Using a Cox proportionate hazards model, it was inferred that APOE e2 and e4 exerted independent effects on recurrence. When the previous occurrence of hemorrhagic stroke was added to the model, the effect of APOE e2 was reduced below cutoffs for statistical significance, while the effects of e4 remained significant. Although no clear relationship was found between the number of copies of e2 or e4 and risk of recurrence, the number of subjects studied may have been too small to discern gene dose effects. O'Donnell et al suggest that determination of APOE genotype might be clinically useful for assessing prognosis of future hemorrhage among patients who have already had one or more such events.

COMMENTARY

Lobar intracerebral hemorrhage accounts for as much as one-third of all nontraumatic hemorrhage strokes and has its highest incidence among the elderly. Recurrence results in significant morbidity and mortality. No proven treatment or preventative strategy for CAA has yet to be found and management is empiric, involving control of hypertension and reduction of other stroke risk factors. The implication of a genetic factor in recurrence of cerebral hemorrhage could contribute to better understanding the underlying disease and may accelerate the process of discovery of new treatment.

The current circumstances, however, are in many respects reminiscent of those that exist for Alzheimer's disease (AD). As many *Neurology Alert* readers know, APOE e4 is a proven risk factor for AD; however, APOE genotyping is not recommended for the purposes of predicting AD largely because no curative treatment or prevention is yet available. O'Donnell et al acknowledge that APOE genotype alone is an imperfect predictor of recurrent lobar intracerebral bleeding, and that multiple genetic and environmental factors are likely to be involved. Extrapolating from the precedent of AD, it seems unlikely that APOE genotyping will enjoy immediate and widespread use as a means of predicting future recurrence of lobar hemorrhage, at least until a treatment becomes available. **—nrr**

Hypotension and Incontinence in Late Parkinsonism

ABSTRACT & COMMENTARY

Source: Wenning GK, et al. Time course of symptomatic orthostatic hypotension and urinary incontinence in patients with postmortem confirmed parkinsonian syndromes: A clinicopathological study. *J Neurol Neurosurg Psychiatry* 1999; 67:620-623.

Neurologists and movement disorders physicians face a constant challenge to differentiate Parkinson's disease (PD) from other neurodegenerative illnesses that cause parkinsonism. Grouped as "parkinson-plus" syndromes, this list includes multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBGD), and diffuse Lewy body disease (DLBD). In this paper, Wenning and colleagues report on the use of two clinical complaints—orthostatic hypotension and urinary incontinence—in the differential diagnosis of parkinsonism.

Seventy-seven pathologically confirmed parkinsonian cases formed the basis for this study. Wenning et al examined the latency to onset, and duration from onset to death, of two autonomic complaints—symptomatic orthostatic hypotension and urinary incontinence. They found that the latency to onset of orthostatic hypotension was much longer in PD (166 months) than in any other cause of parkinsonism (30 months, on average). Similarly, latency to onset of urinary incontinence was longest in PD (144 months), of intermediate duration in PSP and CBGD, and of shortest duration in MSA (12 months). Assigning a one-year latency to symptom onset as a diagnostic cutoff, the positive predictive value of symptomatic orthostatic hypotension was 75% in MSA. In this series, no patients with PD, CBGD, or DLBD developed symptomatic orthostatic hypotension within the first year. The positive predictive value of urinary incontinence was 56% in MSA.

COMMENTARY

This study, while important, is limited by several methodological flaws. There is unavoidable selection bias in any postmortem series, with a tendency to receive severely affected cases. Further, the data were collected retrospectively by reviewing clinical records, a notoriously unreliable proposition. Further, symptoms were not correlated with autonomic measurements, such as abnormal tilt-table testing or rectal EMG.

Despite these problems, this study offers several important lessons. First, latency to onset of two symptoms—symptomatic orthostatic hypotension and urinary incontinence—was helpful in distinguishing PD from other causes of parkinsonism. Second, the early appearance of orthostatic hypotension or urinary incontinence strongly suggested MSA, as opposed to other parkinsonian syndromes.

Does an accurate early diagnosis of MSA, PSP, CBGD, or DLBD help in the clinical management of these disorders? Since there is no therapy that affects the natural history of these disorders, and treatment is often only partially effective, one could argue that an accurate diagnosis is of limited importance except for academic interest. However, patients with MSA pose several challenges that warrant an attempt to secure an early diagnosis. First, as many as one-third of these patients respond to levodopa when given at adequate dose, often for many months. Second, identifying early autonomic dysfunction allows the clinician to protect patients from severe orthostasis by using Florinef and/or Midodrine. These agents allow levodopa to be administered at a dose adequate to achieve an antiparkinson effect, even in the presence of symptomatic orthostasis. Finally, patients with MSA are prone to vocal cord dysfunction, causing stridor and even occasionally nocturnal sudden death. Early recognition of these problems can lead to interventions that improve the quality and length of patients' lives. **—steven frucht, md**

Does Warfarin Reduce Stroke?

ABSTRACT & COMMENTARY

Source: Pullicino PM, et al. Stroke in patients with heart failure and reduced left ventricular ejection fraction. *Neurology* 2000;54:288-294.

The role of warfarin in the prevention of stroke from atrial fibrillation (AF) is well established. Anticoagulation for stroke prevention in cardiac failure, an even more common condition than AF, is also commonly used. No randomized trial has been done to support this practice, however. Pullicino and colleagues review the literature outlining the risk of stroke in cardiac failure, the possible benefits of prophylactic warfarin therapy, and the proposed randomized studies to further explore these questions.

Stasis of blood in a poorly functioning left ventricle may lead to thrombus formation and embolic stroke. The relative risk of stroke is as much as 4.1 times higher among patients with cardiac failure than those without. This risk increases proportionately with decreased ejection fraction. In the Survival and Ventricular Enlargement (SAVE) Trial, there was an 18% increment in stroke risk for every 5% decline in ejection fraction (EF). In the SOLVD Trial (among women), there was a 58% increase in the risk of thromboembolic events for every 10% decrease in EF. No significant increase in stroke rate among men was observed. Comorbid factors such as advanced age, hypertension, and diabetes magnify stroke risk in cardiac failure just as these factors also increase stroke risk in AF.

Cardiac failure is increasingly common, in part due to prolonged survival rates. While patients with severe cardiac failure previously had mortality rates as high as 17% per year, the addition of drug therapy with angiotensin-converting enzyme inhibitors and beta-blockers has reduced this to approximately 5% per year. First-ever strokes attributable to cardiac failure may be as many as 72,000 per year.

Studies of warfarin in patients with a history of myocardial infarction (MI) show relative decreases in stroke risks in the range of 40-55% compared with placebo, about twice the efficacy of aspirin. Data from the SOLVD study suggest that warfarin may also reduce mortality by about 20%. This benefit is likely to be present whether the cardiomyopathy is ischemic or not and is probably independent of the coexistence of AF.

As Pullicino et al outline, warfarin in patients with cardiac failure may have benefit in three main areas: overall mortality reduction, primary stroke prevention, and secondary stroke prevention. But is warfarin justified over aspirin given its possible serious hemorrhagic complications? For first-ever strokes, with an occurrence rate of 1.5% per year and a relative risk benefit of 30%, the absolute risk reduction would be 0.45% per year. This is not significantly higher than the rate of intracerebral hemorrhage (ICH) with warfarin therapy (about 0.3%). For recurrent stroke, the data are more convincing. Because this event is more frequent (about 9% per year), the absolute risk reduction would be 3%, outweighing the risk of ICH by 10-fold.

COMMENTARY

Given the relatively small potential benefit of warfarin for first-ever stroke and the infrequent occurrence of this event among the population at risk, randomized studies would require as many as 10,000 patients to achieve statistical significance. Such limitations have led investigators to suggest using composite endpoints (including cardiac outcomes and overall mortality) or to restrict study to the patients at highest risk (such as those with prior stroke). The table outlines the main features of the proposed Antiplatelet Therapy in Chronic Heart Failure (WATCH) and the Wafarin Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) studies. To decrease sample size, WATCH will include MI in a composite endpoint and WARCEF will include only patients with prior stroke. Pooled data from these two studies combined may have the statistical power to answer specific questions about stroke risk. *Neurology Alert* eagerly awaits these results. **—azs**

Table

Main Features of the WARCEF and WATCH Studies

Feature	WATCH	WARCEF
Blinding	Aspirin and clopidogrel blinded; warfarin unblinded	Blinded
Study	Three (warfarin,aspirin,clopidogrel)	(warfarin, aspirin)
Target INR	2.5-3.0	2.5-3.0
NYHA class for entry	II, III, or IV	I, II, or III
Entry objection fraction	≤ 30%	≤ 30%
Echo entry criteria	LV end diastolic dimension ≤ 6 cm (men) or ≤ 5.6 cm (women) and fractional shortening < 22%	Wall motion index ≤ 2
Primary endpoint	Death, stroke, and myocardial infraction	All-cause mortality and stroke
Study duration	5-y with 3-y enrollment	5-y with 3-y enrollment
Sample size	4500 patients	2860 patients

INR= International Normalized Ratio; LV = left ventricular; NYHA = New York Heart Association; WARCEF = Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction; WATCH = Warfarin and Antiplatelet Therapy in Chronic Heart Failure

Source: Pullicino PM, et al. *Neurology* 2000;54:293.

Polyneuropathy in Diabetes Mellitus, Type 1

ABSTRACT & COMMENTARY

Source: Christen WG, et al. Risk factors for progression of distal symmetric polyneuropathy in type 1 diabetes mellitus. *Am J Epidemiol* 1999;150:1142-1151.

Among patients older than 30 years and suffering insulin-required type 1 diabetes, as many as 60% will sooner or later develop distal, symmetric polyneuropathy. No direct therapy or anticipatory medications have as yet appeared either to decrease its incidence or slow its progression. Risk factors, however, have been identified and are carefully identified and discussed by Christen and colleagues.

The initial study from which complications were identified involved 497 type 1 diabetics collected from 22 clinical centers. Their ages ranged from 18-56 years on entry and insulin treatment had ranged between 1-15 years. The study target was to determine whether sorbital, an aldose reductase inhibitor, would reduce the usual 60% risk that type 1 diabetics would develop distal symmetric polyneuropathy by age 31 years. The results were recorded in two papers (*Ann Intern Med* 1995;122:561-568; *Neurology* 1993;43:1141-1149). Relative risks of neuropathy among participants were identified as 1) having increased percentage levels of glycosylated hemoglobin (GSH) during the trial and 2) giving a history of ever being cigarette smokers. The present reanalysis added additional risk factors to the original findings. These included: entry risk factors for DSP in type 1 diabetes included age older than 30 years at onset, had a disease experience of more than 15 years, an elevated blood pressure, elevated serum cholesterol, smoking at any time, height greater than average, and female gender. GSH levels lying between 10.2 and 13.5 tripled the incidence of DSPs, whereas those with GSH levels more than 13.5% ran a six-fold risk of having severe type 1 diabetic neuropathy.

COMMENTARY

Type 1 diabetes results from an autoimmune disorder that attacks and destroys the beta-insulin-generating cells of the pancreas. This in itself leads to varying glucose concentrations in the body, making difficult protective efforts for stabilizing blood glucose levels. *Neurology Alert* urges physicians and neurologists to make every effort to keep total glycosylated hemoglobin below 10.2 so as to prevent severe retinopathy or neuropathy in patients with type 1 diabetes. This article additionally emphasizes the above newly established qualities as risk factors to preceding reports. **—fp**

CME Questions

7. On electrodiagnostic studies:

a. sensory nerve conduction velocities are slowed significantly and more frequently in hereditary neuropathy with liability to pressure palsies (HNPP) than in chronic inflammatory demyelinating polyneuropathy (CIDP) or diabetes.
b. respiratory synkinesis ("breathing arm"), with bursts of motor unit activity in one or more arm muscles synchronous with respiration, is seen in 50% of syringomyelia patients.
c. complex repetitive discharges, even in the absence of positive waves or fibrillation potentials, are strongly predictive of inflammatory histology on muscle biopsy.
d. x-linked dominant Charcot-Marie-Tooth disease (CMTX) is predominantly axonal in nature but has the unique characteristics of acquired demyelinating disease of temporal dispersion and nonuniform slowing.
e. All the above are false

8. Risk of recurrent lobar intracerebral hemorrhage from cerebral amyloid angiopathy is significantly:

a. increased by a history of diabetes and hypertension.
b. decreased by possession of APOE e2 or e4.
c. unchanged by a past history of lobar hemorrhage.
d. affected by APOE e2 and e4 independently.
e. greater in females than males.

9. In medically treated patients with severe ICA stenosis, the annual risk of hemispheric stroke in the presence of collaterals is approximately:

a. 50%.
b. 30%.
c. 28%.
d. 11%.
e. 5.5%.

10. Mitoxantrone:

a. recently received an FDA advisory panel recommendation for treating progressive forms of MS.
b. may only provide short-term control of MS disease activity.
c. is not possible to use for extended periods.
d. needs a more complete assessment of long-term risks.
e. All of the above

In Future Issues:

Spontaneous and Reflex Movements in Brain Death