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INSIDE

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Repetitive Transcranial Magnetic Stimulation for Tinnitus: An Evolving Therapy

ABSTRACT & COMMENTARY

By Douglas Labar, MD, PhD

Director of the Comprehensive Epilepsy Center, Professor of Neurology and Neuroscience, Weill Cornell Medical College; Attending Neurologist, NewYork-Presbyterian Hospital

Dr. Labar reports no financial relationship relevant to this field of study.

Synopsis: *Transcranial magnetic stimulation of the brain may be a promising new therapy for the treatment of chronic tinnitus.*

Source: Khedr E, et al. Contralateral versus ipsilateral rTMS of temporoparietal cortex for the treatment of chronic unilateral tinnitus: Comparative study. *European J Neuro* 2010; DOI 10.1111/j.1468-1331.2010.02967.x. (Published online 3/3/10.)

CHRONIC TINNITUS MAY BE DISABLING, AND ALWAYS IS DIFFICULT TO TREAT. In some patients, this symptom may be analogous to phantom limb pain, in that hearing loss produces functional de-afferentation of auditory cortex and leads to excess cortical excitation. Focal repetitive transcranial magnetic stimulation (rTMS) of cerebral auditory areas may disrupt abnormal neuronal excitatory circuitry and reduce tinnitus symptoms.

Which side of the brain should receive magnetic stimulation? Increased left-side cortical activity has been shown in one study, employing positron emission tomography in tinnitus cases.[1] On the other hand, functional MRI revealed greater reactivity to auditory stimuli in the hemisphere ipsilateral to lateralized tinnitus symptoms.[2] This suggests that the hemisphere contralateral to the tinnitus is abnormally active at baseline, and less reactive to exogenous stimuli. Khedr and colleagues set out to study whether contralateral or ipsilateral rTMS of temporoparietal cortex provided superior relief of unilateral tinnitus.[3]

Sixty-two patients affected with unilateral tinnitus for up to 10 years were treated with two consecutive five-day courses of rTMS.

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They were randomized to receive treatment on the side of the brain ipsilateral or contralateral to their symptoms. The patients were unaware that laterality of the therapy was under investigation, and neurologist investigators were blinded as to the patients' treatment groups. Patients were assessed with the tinnitus handicap inventory (THI) and the Hamilton ratings of depression and anxiety prior to the 10 days of treatment, after treatment, and monthly for the next 10 months.

There was an immediate significant reduction in the THIs seen in the first assessments at the end of the 10-treatment therapy period. This occurred only with stimulation contralateral to the unilateral tinnitus. Contralateral stimulation was superior to left-side stimulation, and there was no difference between left- and right-side stimulation. Depression and anxiety severity scores, which correlated with THI severity at baseline, improved correspondingly.

Remarkably, after only 10 treatment sessions over two weeks, the clinical improvement persisted unabated for the next 10 months without further therapy. This contrasts with results of rTMS for seizures, where the antiepileptic effects wear off after two months.[4]

■ COMMENTARY

The time course of these rTMS results for tinnitus also can be compared with outcomes of rTMS for treatment-resistant depression, which recently has been cleared by the U.S. Food and Drug Administration for clinical use.[5] In a large clinical trial, 53/136 initial responders required additional therapy within 24 weeks.[6] A small early study suggested antidepressant effects last less than 14 days.[7]

Thus, a single course of rTMS of temporopatietal cortex contralateral to chronic unilateral tinnitus symptoms may permanently reorganize underlying abnormal auditory cortex functions. It may not just temporarily suppress the patients' symptoms, as seems to occur in other conditions where rTMS therapy has been tried. Several editorials have suggested rTMS is rapidly approaching being an accepted avenue of care for this illness.[8,9]

Finally, electrical stimulation of auditory cortex via chronic implanted electrodes may be even more efficacious for pure tone tinnitus than rTMS (97% vs. 77% reduction in 12 patients).[10] If supported by larger follow-up clinical trials, direct electrical brain stimulation for tinnitus may become an even more effective treatment than rTMS for this sometimes disabling condition.

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New Developments in Attentional Rehabilitation

ABSTRACT & COMMENTARY

By Marc Dinkin, MD

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Dr. Dinkin reports no financial interest in this field of study

Synopsis: *The presence of conjugate eye deviation as measured by CT or MRI in acute stroke patients predicts visuo-spatial neglect. Prismatic therapy produces a cross-modality improvement in left-sided auditory extinction in patients with chronic right-sided stroke.*

Sources: Becker E, et al. Neuroimaging of eye position reveals spatial neglect. *Brain* 2010:133:909-914; Jacquin-Courtois S, et al. Effect of prism adaptation on left dichotic listening deficit in neglect patients: Glasses to hear better? *Brain* 2010:133;895-908.

SPATIAL NEGLECT IS A RELATIVELY COMMON FINDING IN PATIENTS who have suffered a right-hemisphere acute stroke and has the potential to severely affect daily functioning and quality of life. Visuo-spatial neglect may be measured using clinical tests such as letter cancellation, but such tasks are time consuming and may not feasible in patients who are too debilitated to participate. It has been found that the presence of ipsilesional conjugate eye deviation (CED) correlates with the size of hemispheric lesions involving the right middle and superior temporal gyri. Electro-oculography has shown CED in patients with left-sided spatial neglect, but this technique is not easily available in the inpatient setting. CT scans, which are already acquired in acute stroke, offer an alternative method of measuring CED, and were utilized by Simon et al to predict lesion side.

Becker and colleagues used CT or MRI images at presentation to investigate whether CED could distinguish patients with hemispheric strokes and spatial neglect from those that did not have neglect. Among 71 patients, the average degree of ipsilesional CED was significantly higher in those with spatial neglect (~10°) than those who simply had hemispheric lesions, (< 5°). Lesion size was used as a covariate factor, ameliorating the confounding effect that CED might be more likely to occur with larger lesions, which in turn might be associated with neglect. Finally, the inclusion of the right superior and middle temporal gyri in the lesion area correlated better with the degree of CED than any other location, although the effect was not significant.

One rehabilitative strategy for patients with left visuo-spatial neglect due to right hemispheric lesion involves the use of bilateral prisms, which shift the visual world to the right by 10°. The patient is then asked to point at a series of 50 targets located in both sides of the midline. Over the session, this therapy leads to a recalibration of the visuo-proprioceptive map and has been shown to improve visual hemispatial neglect. Jacquin-Courtois and colleagues investigated whether or not this prismatic adaptation could also lead to improvement in left-sided auditory neglect in patients with chronic right hemispheric strokes. Dichotic auditory stimuli (two words heard simultaneously in right and left earphones) were presented to patients with left-sided auditory neglect, and a laterality index was generated representing the asymmetry of correctly identified words. Surprisingly, one session of prismatic shift therapy led to a significant amelioration in left auditory extinction at both 0 and 2 hours post-therapy, while sham therapy with non-prismatic goggles did not.

■ COMMENTARY

Becker's study has powerful clinical implications, as it suggests that brain imaging, which is already performed in every stroke patient, can be used to predict the presence of spatial neglect without any need for patient cooperation or additional clinical testing. This finding could lead to earlier recognition and even quantification of spatial neglect, although they have not yet shown that the degree of deviation correlates well with the degree of neglect. Although the association between CED and neglect has already been shown in EOG studies, the demonstration of this principle using neuro-imaging adds to the credibility of this more practical methodology.

The authors did not address the presence of visual field defects in 20% of the patients with right hemispheric lesions and spatial neglect. Could such a field defect contribute to ipsilesional CED as patients searched the available visual landscape? This is unlikely, since patients without spatial neglect were more likely to have a field defect in this study, and still showed less CED. Nevertheless, the conclusions would have been strengthened by including visual field defect as a covariate in their analysis and by the use of more sensitive formal visual field analysis.

Jacquin-Courtois's results support the notion that adaptation of neglect in response to prismatic therapy is modulating higher order determinants of spatial orientation that are not specific to visual or proprioceptive modalities. When patients learn to recalibrate visual to proprioceptive stimuli during the therapy, this change appears to apply to auditory mapping as well. The effects of auditory neglect are increasingly recognized, and may be particularly troublesome for patients with low vision who may use auditory clues to navigate and for social interactions. The clinical importance of this study, therefore, lies not only in what it says about the neuro-anatomical basis of prismatic adaptation, but in that it offers a feasible and efficacious therapy to these patients.

With earlier recognition and quantification of visual neglect using neuro-imaging and the use of a novel means of treating auditory neglect with the established therapy of prismatic shift, these studies together may lead to real improvements in the post-stroke care of patients with spatial neglect.

Levetiracetam in Newly Diagnosed Glioma, Epilepsy

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD

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Dr. Kandula reports no financial interest in this field of study

Synopsis: *This prospective case series reports on the efficacy and safety of levetiracetam in central nervous system gliomas.*

Sources: Rosati A, et al. Efficacy and safety oflevetiracetam in patients with glioma: A clinical prospective study. *Arch Neurol* 2010;67: 343-346.

Seizures may occur as the initial presentation or later in the medical course of a primary brain tumor. The treatment of central nervous system glioma patients is multimodal, requiring the use of anti-epileptic agents, systemic steroids, and chemotherapeutics. Thus, anti-seizure medications such as levetiracetam with no clinically relevant drug interactions and lack of hepatic P-450 induction or inhibitory effects is very desirable. Although levetiracetam has been used extensively in both the United States and Europe in glioma patients, few long-term studies assessing the efficacy of the medication are available. The authors of this study present the clinical treatment response of newly diagnosed glioma patients with epilepsy.

Only newly diagnosed glioma and epilepsy patients were included in this clinical prospective trial. Patients previously on anti-epileptic agents or prior diagnosis of glioma were excluded. Epilepsy was defined as either recurrent clinical seizures with or without interictal epileptiform abnormalities (IEAs) on electroencephalogram recording, single focal or convulsive seizure with associated IEAs, single convulsion and history of prior episodes suggestive of focal seizures with or without IEAs, or seizures occurring de novo during medical follow up with or without IEAs. Patients were then treated with initial dosages of either 500 mg bid (< 70 years of age) or 250 mg bid (>70 years of age) of levetiracetam.

At subsequent follow up visits (every 1-3 months), seizure recurrence and causative factors were assessed. Seizure recurrence was categorized as either daily, weekly, monthly, rare (< 1 seizure per month), or no seizures. Cause of seizure recurrence was categorized as follows:

1. radiographic tumor recurrence after prior radiographic response;
2. malignant (radiographic or pathologic) tumor progression;
3. subtherapeutic anticonvulsant levels in the absence of clear tumor progression and cessation of seizures with dose increase;
4. refractory seizures that occurred despite optimal therapeutic anticonvulsant levels and absence of tumor recurrence; or
5. radiotherapy induced seizures. Seizures secondary to causes 1-3 were treated with levetiracetam dose increase.

Condition 4, refractory seizures, was treated with add on treatment with either oxcarbazepine, topiramate, or valproic acid. Radiotherapy induced seizures were treated only with corticosteroids. All patients were categorized based on the extent of neurosurgical resection (neurosurgeon report and post contract CT scan) as partial (< 50%), subtotal (50%–80%) or total tumor removal.

Out of the 176 consecutive newly diagnosed glioma patients in the nearly three-year study, 82 patients had epilepsy and met study criteria. In 75 of 82 patients (91%), epilepsy was the presenting symptom and nearly two thirds of enrolled patients had grade IV glioma; 75 of 82 patients were seizure-free at the last evaluation either with monotherapy with levetiracetam (73 patients), topiramate (1 patient), or valproic acid (1 patient). The mean follow-up time was 13.1 months. Levetiracetam was stopped in the above two patients receiving topiramate and valproic acid monotherapy due to intolerable side effects. In the 7 of 82 drug-resistant patients, all patients were either grade III or IV.

■ COMMENTARY

The results of this study suggest that levetiracetam is safe and effective for primary brain tumors with epilepsy. The authors found no definite laboratory abnormalities associated with concomitant use of levetiracetam and chemotherapeutic agents (temozolomide and fotemustine). Nearly 90% of patients achieved seizure control with levetiracetam monotherapy . Nearly two-thirds of these patients achieved control with levetiracetam doses of 1500-3000 mg per day, suggesting that moderate dosing of this agent may be efficacious.

Despite widespread use of levetiracetam, the exact mechanism of action is still not clear. The most recent evidence

points to SV2A (synaptic vesicle protein) as the brain-binding site for levetiracetam. This glycoprotein has been suggested as a modulator of vesicular fusion and synaptic vesicular release (prevention of exocytosis of excitatory glutamate). Furthermore, whether levetiracetam has any inherent mechanistic properties that are useful in brain tumor patients also needs elucidation. An article by Haghikia et al suggests, in animal models, that levetiracetam has the ability to prevent astroglial dysregulation under inflammatory conditions as might be seen in recurrent seizures.[1]

Although levetiracetam is currently not FDA-approved in the United States as monotherapy, its lack of drug interactions, efficacy, and safety profile suggest that the medication be considered in glioma patients, particularly in patients who demonstrate side effects from other FDA approved monotherapy anticonvulsants. In the interim, slowly accumulating evidence suggests the safety of levetiracetam, but head-to-head efficacy comparisons with other anticonvulsants, particularly other second-generation anticonvulsants are still needed.

Reference

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Prognostic Factors in a Large Cohort of Patients with Glioblastoma

ABSTRACT & COMMENTARY

By Adília Hormigo, MD, PhD

Attending Neurologist, Memorial Sloan-Kettering Cancer Center, and Assistant Professor of Neurology, Weill Medical College of Cornell University

Dr. Hormigo reports no financial relationships relevant to this field of study.

Synopsis: *This large retrospective study reports an overall poor prognosis for patients with GBM, but treatment was not "state-of-the-art."*

Source: Helseth R, et al. Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. *Acta Neurol Scand* DOI:10.1111/j.1600-0404.2010.01350.x.

GLIOBLASTOMA (GBM) IS THE MOST COMMON AND MALIGNANT of all primary brain tumors. The initial standard treatment is resection followed by radiotherapy with concurrent chemotherapy with temozolomide and then adjuvant temozolomide. The median survival with treatment is about 12-14 months. However, in patients whose tumor tissue contains promoter methylation of MGMT (O6-methylguanine–DNA methyltransferase) DNA repair gene, survival can reach 24 months. The epigenetic silencing of this gene renders the tumor to be sensitive to alkylating agents.

In this paper, the authors retrospectively reviewed the cases of 516 consecutive patients who underwent the initial surgery for their GBM at Oslo University Hospital between the years 2003 and 2008. The median overall survival for those patients was 9.9 months. The authors identified as poor prognostic factors age greater than 60, poor neurological function, bilateral brain involvement, biopsy instead of resection, and adjuvant treatment with radiotherapy without concomitant use of chemotherapy with temozolomide. Sixty-five patients (13%) underwent repeat surgery and had an overall survival of 18.4 months. The indications for reoperation were worsening of neurological deficits (35.4%), raised intracranial pressure (33.8%), tumor progression on MRI (20%), and seizures (11%).

■ COMMENTARY

This is a large, single-institution, retrospective study looking at prognostic factors for GBM. Analysis in such studies has limitations found in all retrospective work. Specifically for this study, the regimen of radiotherapy changed during the course of the years, from a total dose of 48 Gy given in two daily fractions to a more conventional daily treatment to a total of 60 Gy. This may be one of the reasons accounting for their low overall survival. We also do not know the extent of resection for the patients who underwent surgery and not just biopsy of their tumor. Post-operative MRI was not performed initially in the study in over half of the patients. The treatment regimen was not consistent, with only about half the patients having received radiotherapy with concurrent chemotherapy. The treatment was less aggressive for the elderly and it has been shown that at least the use of radiation for patients 70 and older has significant survival benefit without worsening of quality of life and cognition. The state of the art of analysis of MGMT promoter methylation status in tissue blocks, for purpose of determination of prognosis for survival was not performed in any group of patients. The improved survival on patients who underwent reoperation is most likely the result of several factors, including selection for surgery of patients whose tumor is still amenable to surgical resection, better performance status and younger age. It is unclear, in patients whose indication for surgery was seizures, what type of surgery they had, whether reoperation for the tumor, or surgery for epilepsy, and if it was or was not beneficial.

This study confirms the factors known to influence sur-

vival. We will only be able to further clarify prognostic factors for GBM by conducting prospective trials.

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1. Hegi ME, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Eng J Med* 2005;352:997-1003.
2. Keime-Guibert F, et al. Radiotherapy for glioblastoma in the elderly. *N Eng J Med* 2007;356:1527-1535.

Spinal Sarcoidosis

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports no financial relationships relevant to this field of study.

Synopsis: *Spinal cord sarcoidosis is difficult to diagnose and may be confused with multiple sclerosis and neuromyelitis optica. Treatment response is variable.*

Source: Cohen-Aubart F, et al. Spinal cord sarcoidosis: Clinical and laboratory profile and outcome of 31 patients in a case-control study. *Medicine* 2010;89;133-140.

Sarcoidosis, an idiopathic multisystem granulomatous disorder with a prevalence of 1-40/100,000 population, affects the nervous system in 5%–16% of cases, and the spinal cord in less than 1%. Differentiating sarcoid from other causes of myelopathy is challenging and this retrospective, multi-center, case-control study was undertaken to further its understanding by describing the clinical, laboratory, and magnetic resonance imaging (MRI) features of spinal sarcoid, its morbidity, long-term sequelae, and prognosis.

Between 1993 and 2006, 31 patients with spinal cord sarcoidosis were seen by the departments of Neurology, Medicine, and Pulmonology at Pitie-Salpetriere and Avicenne Hospitals in Paris and Bobigny, France, respectively. Inclusionary criteria included myelopathic presentation based on motor, sensory, sexual, and/or sphincteric symptoms and signs below a spinal cord level, spinal cord MRI revealing an intramedullary lesion, noncaseating granulomata on biopsy or elevated lymphocyte levels on bronchioalveolar lavage (BAL), and no other preferred diagnosis. Laboratory studies included chest X-ray, pulmonary function tests, thoracic computed tomography (CT) scans, bronchoscopy, tissue biopsies, histologic analyses, serum angiotensin-converting enzyme (ACE), cerebrospinal fluid (CSF) analysis, and spinal cord and brain MRI. Clinical course was categorized as monophasic, remitting-relapsing (intermittent flares with no progression between flares), or progressive with or without flares. Patients seen between 1999 and 2006 with clinical myelopathy, spinal MRI with an intramedullary abnormality, and laboratory features suggesting a diagnosis other than sarcoid, usually multiple sclerosis or neuromyelitis optica, served as controls (n = 30). Statistical analyses comprised the chi-square, Fisher exact and Mann-Whitney tests, and P values < 0.05 were considered significant.

Among 31 spinal sarcoidosis patients, mean age of onset was 41.6 years, with a mean of 15.1 months between symptom onset and diagnosis. Most (65%) were men, white (61%), with spinal sarcoid the initial presentation in 90%, most often subacute (74%) in onset. Extraneurologic sarcoid was present in 22, involving the lung and mediastinal lymph nodes (n = 17, 77%), liver (n = 10, 45%), peripheral lymph nodes, eye, or skin (n=2, 9% each), and arthritis, bone or sinuses (n= 1, 5% each). Significant findings in the sarcoid group, compared to controls, included elevated serum C-reactive protein (CRP) (54% vs. 7% controls), lactate dehydrogenase (LDH) (53% vs. 0% controls), and ACE (39% vs. 13% controls), lymphopenia (50% vs. 3% controls), and hypergammaglobulinemia (33% vs. 7% controls), with elevated CSF protein and white blood cell count and low CSF glucose. No difference between patients and controls was found on liver function tests, serum calcium, or CSF ACE level or oligoclonal bands. Lymph node biopsy was most sensitive (8/8), whereas bone marrow and muscle biopsy were least sensitive (0/9). BAL lymphocytosis with CD4/8 >3.5 was present in 15/18. Among 26 patients who underwent spinal MRI, all demonstrated T2-weighted hyperintensity lesions

CME Objectives

Upon completion of this educational activity, participants should be able to:

1. discuss current scientific data regarding the diagnosis and treatment of neurological disease;
2. discuss the pathogenesis and treatment of pain;
3. describe the basic science of brain function;
4. discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
5. identify nonclinical issues of importance for the neurologist.

CME Questions

- Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.
- After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

in the thoracic (n = 17) or cervical (n = 15) region, which enhanced in 74%, and were often heterogeneous (31%), and multifocal (27%). Other than T2 extension along multiple vertebral bodies (6 vs. 2 in controls), these findings were not unlike those of controls. Brain MRI was abnormal in 55% of spinal sarcoid patients compared to 23% of controls (P = 0.01). Approximately one-third each had a monophasic, remitting-relapsing, or progressive course with or without flares despite treatments including corticosteroids, cyclosporine, cyclophosphamide, methotrexate, mycophenolate mofetil, and hydroxychloroquine. Spinal sarcoid remains a diagnostic challenge but MRI, CSF and serum CRP and LDH, in addition to biopsy of appropriate tissue, may assist in its accurate diagnosis.

■ **COMMENTARY**

Trans-esophageal, endoscopic, ultrasound-guided, fine-needle aspiration (EUS-FNA) of mediastinal lymph nodes may be a relatively less invasive, yet high yield, method of obtaining tissue for the diagnosis of sarcoid (Endoscopy 2010;42:213-7). Retrospective study was undertaken of 101 consecutive patients with suspected pulmonary sarcoidosis who underwent EUS-FNA of mediastinal lymph nodes with 22-gauge needles. Both cell-block analysis and conventional cytological evaluation were utilized. Over half had previously undergone non-diagnostic bronchoscopy. EUS detected granulomas in 87% by either cytology or cell-block analysis when employed together, and in 6 cytology-negative patients (33%), granulomas were present in the cell-block. Only 1 patient developed mediastinitis. EUS-FNA can reduce the number of mediastinoscopies required for the diagnosis of sarcoidosis.

CME Questions

47. Transcranial magnetic stimulation has been demonstrated to be safe and effective in the treatment of drug-resistant depression.
a. True
b. False

48. Jacquin-Courtois et al found that prismatic therapy:
a. led to an improvement in visual neglect without an effect on the auditory realm.
b. led to an improvement in auditory neglect right after the treatment but not at 2 hours.
c. led to an improvement in auditory neglect right after treatment and at 2 hours.
d. improved ipsilesional hearing as measured by standard audiometry.
e. improved visual neglect but worsened auditory neglect.

49. All of the following are true about levetiracetam *except:*
a. Levitiracetam does not induce the metabolism of drugs sensitive to hepatic P-450 enzymes.
b. Levitiracetam has an excellent safety profile.
c. Levitiracetam has been proven effective as monotherapy in randomized, controlled, clinical trials.
d. Levitiacetam has been approved as adjunctive therapy for partial epilepsy.

50. Which of the following is true for patients with glioblastoma?
a. Radiotherapy does not improve survival in the elderly.
b. Bilateral involvement of the brain by the tumor has no implications on patient survival.
c. The finding of unmethylated MGMT promoter results in inactivation of MGMT repair gene.
d. MGMT promoter methylation is an indicator of response to temozolomide.

51. Compared to other forms of myelopathy, spinal sarcoidosis
a. more often has elevated serum C-reactive protein (CRP), lactate dehydrogenase (LDH), and ACE.
b. more often has lymphopenia and hypergammaglobulinemia.
c. more often has elevated cerebrospinal fluid (CSF) protein and white blood cell count and low CSF glucose.
d. more often has T2 extension along more than two vertebral bodies on spinal cord magnetic resonance imaging (MRI).
e. All the above are true

52. Therapeutic hypothermia has been shown to improve outcome from ischemic stroke.
a. True
b. False

Answers: 47. a, 48. c, 49. c, 50. d, 51. e, 52. b

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, *MD, Interim Chair and Neurologist-in-Chief, Director, Division of Stroke & Critical Care Neurology, Weill Cornell Medical College and New York Presbyterian Hospital.*

Dr. Fink reports no financial relationships relevant to this field of study.

Warfarin-treated patients who receive TPA have a much higher risk for symptomatic intracerebral hemorrhage (ICH).

Prabhakaran S, et al. Symptomatic intracerebral hemorrhage among eligible warfarin-treated patients receiving intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol* 2010;67: (doi:10.1001/archneurol.2010.25).

THE AUTHORS REVIEWED RECORDS OF 107 PATIENTS WHO WERE treated with intravenous TPA according to a standard protocol that required an INR < 1.7. Baseline warfarin use was present in 12.1% of all patients but the median INR = 1.04 (range 0.82–1.61). The overall rate of symptomatic ICH was 6.5%, but it was nearly 10-fold higher among patients taking warfarin compared to those not taking war-

farin at baseline (30.8% vs 3.2%, respectively; p = .004) after adjustments for age, atrial fibrillation, NIH Stroke Score, and INR. Therefore, any use of warfarin, even with an INR that is in the normal range, increases the risk of ICH. In these situations, IV TPA should be given with the greatest caution and close monitoring.

Fever with ischemic stroke — good or bad?

Prasad K, et al. Fever is associated with doubling of odds of short-term mortality in ischemic stroke: an updated meta-analysis. *Acta Neurol Scand* DOI: 10.1111/j.1600-0404.2010.01326.x. Naess H, et al. Inverse relationship of baseline body temperature and outcome between ischemic stroke patients treated and not treated with thrombolysis: the Bergen stroke study. *Acta Neurol Scand* DOI:1111/j.1600-0404.2010.01331.x.

TWO COMPANION ARTICLES FOCUS ON THE ROLE OF FEVER in patients with acute ischemic stroke. The study by Prasad and colleagues is a meta-analysis that reviewed all studies that examined the relationship between fever in acute ischemic stroke and mortality, from January 1990 to November 2008. Heterogeneity was assessed using I^2 and chi-square statistics and odds ratios (OR) from logistic regression were combined. Six cohort studies involving 2986 patients were included. Meta-analysis revealed a combined OR of 2.20(95% CI 1.59-3.03, $p < 0.00001$) for mortality in the first month. The authors concluded that fever within the first 24 hours of hospitalization in patients with ischemic stroke is associated with doubling of the odds of death within one month of onset of stroke. However, it is not known if the development of fever is a marker for subsequent poor outcome, or may be a contributing cause.

In the Naess et al. study, the authors evaluated the hypothesis that elevated body temperature would enhance the thrombolytic effects of tissue plasminogen activator (TPA) in patients who received this treatment, and low body temperature would be neuroprotective for patients who did not receive TPA. They included 111 patients who received TPA and 139 patients who were not treated with TPA but presented within 6 hours of stroke onset. NIH Stroke Scale was obtained on admission and outcome was assessed using the modified Rankin score (mRS). Using logistic regression analysis, high body temperature was associated with a favorable outcome (mRS 0-2) in patients treated with TPA (OR = 3.7, p=0.009) and low body temperature was associated with favorable prognosis in patients not treated with TPA(OR=2.0, p=0.042), but this barely reached statistical significance.

These conflicting findings about high and low body temperature certainly create a clinical conundrum—thrombolysis is the most effective means to accomplish revascularization in ischemic stroke, and because it is an enzymatic effect, elevated temperature would enhance the potency of TPA. However, many groups are pursuing therapeutic hypothermia as a neuroprotective strategy, along with thombolysis. These conflicting findings point to the importance of answering these questions with well-designed, randomized clinical trials.

What is leukoaraiosis? Ischemia, edema, or inflammation?

Auriel E, et al. Clinical, radiological and pathological correlates of leukoaraiosis. *Acta Neurol Scand* DOI: 10.1111/j.1600-0404.2010.01341.x.

THE IMAGING PICTURE OF LEUKOARAIOSIS (LA) WAS FIRST defined by Hachinski (*Arch Neurol* 1987;44:21-23) based on low-density lesions on CT scans in the white matter of the centrum semiovale, in patients who had vascular risk factors for ischemic stroke. With the advent of MRI, hyperintensities in the white matter on T2 and FLAIR-weighted imaging became even more prominent, and were shown to predict subsequent stroke, but even more important, subsequent cognitive impairment and dementia. The most common risk factor for LA is age, but other vascular risk factors, such as hypertension, diabetes, obesity and metabolic syndrome, were all contributory. What is the pathology that correlates with LA? This is a difficult question because it is difficult to find pathologic material that can be paired temporally with CT or MR imaging.

Auriel and colleagues studied 93 deceased patients who had premortem MRI with T2-weighted images. Tissue specimens were taken from 19 brains that demonstrated severe LA premortem, and these were compared to five control brains. The clinical variables that were found to significantly correlate with LA were age and a history of Parkinson's disease. Other risk factors and markers for atherosclerosis were not significantly correlated with LA, and those included hypertension and diabetes. The histology of the LA lesions did not show staining for any abnormalities of myelin, astrocytes, microglia, smooth muscles cells, or elastin. The lesions were not infarcts and did not show any inflammation. However, there was one consistent finding—thickening of the walls of small arteries and arterioles, sometimes to the point of total occlusion. The authors postulate that LA, as seen on imaging, represents the effects on white matter of chronic hypoxia/ischemia that is not enough to cause cell death or demyelination, but causes functional impairment in neural conduction with increasing age, and increases the risk for infarction.

In Future Issues: **Viral Encephalitis**

Neurology Alert

2010 Reader Survey

In an effort ensure *Neurology Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. *T*he results will be used to ensure you are getting the information.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Return the questionnaire in the enclosed postage-paid envelope by **July 15, 2010.**

In future issues of *Neurology Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	**B. less coverage**	**C. about the same amount**
1. epilepsy	O A	O B	O C
2. behavioral neurology	O A	O B	O C
3. movement disorders	O A	O B	O C
4. pain	O A	O B	O C
5. peripheral neurology	O A	O B	O C
6. stroke	O A	O B	O C
7. trauma	O A	O B	O C
8. basic neuroscience	O A	O B	O C
9. Alzheimer's disease	O A	O B	O C
10. Parkinson's disease	O A	O B	O C
11. multiple sclerosis	O A	O B	O C
12. pathophysiology	O A	O B	O C

13. What other topics would you like to see discussed in *Neurology Alert*? _____

_____

_____

14. Are the articles in *Neurology Alert* written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

15. Are the articles in *Neurology Alert*

O A. Too short O B. Too long O C. About right

16. What type of information not currently provided in *Neurology Alert* would you like to see added? _____

_____

_____

Please rate your level of satisfaction with the items listed.

	A. excellent	B. good	C. fair	D. poor
17. quality of newsletter	O A	O B	O C	O D
18. article selections	O A	O B	O C	O D
19. timeliness	O A	O B	O C	O D
20. quality of commentary	O A	O B	O C	O D
21. clearness of abstracts	O A	O B	O C	O D
22. overall value	O A	O B	O C	O D
23. customer service	O A	O B	O C	O D

24. To what other publications or information sources about neurology do you subscribe?

25. Including *Neurology Alert,* which publication or information source do you find most useful, and why?

26. Which web site related to your position do you use most often?

27. Please list the top three challenges you face in your job today.

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O A. private practice O B. hospital O C. government institution O D. research

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O A. yes
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If yes, how? _____

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Health Care Reform Update

What Health Care Reform Means to You A supplement to *Neurology Alert*

Increased provider access tops list of what clinicians will like about HC bill

Changes will take a few years

HEALTH CARE CLINICIANS AND ORGANIZATIONS LIKELY will find that the new health care reform bill's positive features outweigh its drawbacks, experts say.

The Patient Protection and Affordable Health Care Act, signed into law on March 23, 2010, by President Barack Obama, provides a series of changes to take place to health care insurance coverage, Medicare, Medicaid, prescription drugs, quality improvement initiatives, medical malpractice, and other items. These are to be implemented from 2010 to 2014.

"The thing that is so big is the coverage for tens of millions of people who don't have health insurance now," says **Cecil Wilson**, MD, an internist in Winter Park, FL, and the president-elect of the American Medical Association in Chicago, IL.

People no longer will have to worry about losing health care coverage for existing diseases if they lose their jobs, and increasing numbers of people will have access to preventive care, primary care, and disease management, Wilson adds.

"Those are the big things that make this such a sea change in my opinion," he says. "For physicians, this is good because they won't have to worry about their patients' insurance being cut off, and thus putting their patients at risk."

Hospitals will find that significantly more patients will have health care coverage, resulting in a decline in uncompensated care, says **Caroline Steinberg**, vice president for trends analysis for the American Hospital Association of Washington, DC.

"We also would expect that demand for care from formerly uninsured patients will increase," Steinberg says. "Hopefully, we'll see some increases in primary care so by the time they hit the hospital they won't have some of the same kinds of problems they've had before."

The new bill provides billions of dollars in funding for clinics that provide primary care to uninsured, indigent, and immigrant patients. In 2014, it also expands Medicaid to all non-Medicare eligible individuals who have incomes up to 133% of the federal poverty level. These initiatives could help send more people to primary care services and keep them from using the emergency room for non-emergency care, Steinberg adds.

"We may [identify] more people with conditions that require specialty care because once people have access to coverage they tend to use more health care across all levels of the system," Steinberg says. "So that could go either way."

Plus, hospitals should expect the next few years to continue to be rough fiscally since most of the more significant provisions in the bill will not be fully implemented until 2014.

"Our hospitals are telling us that uncompensated care is going up because of job losses and loss of insurance, and these people show up in hospitals," Steinberg says.

There won't be much improvement in the immediate future until the economy recovers and the government provides more funding for Medicaid, she notes.

More oncology patients will have access to care, as a result of the bill's prohibition of lifetime limits on the dollar value of coverage, which begins Jan. 1, 2014. There is a temporary national high-risk pool to provide health care coverage to people with pre-existing medical conditions, which will be in place between June, 2010, and 2014.

"Many cancer patients who need repeated courses of treatment can easily exceed their caps and find themselves unable to afford needed treatment and medication," says **Allen S. Lichter**, MD, chief executive officer of the American Society of Clinical Oncology (ASCO), in a statement issued after the bill was signed.

By this fall, insurers will not be able to exclude children with pre-existing conditions from being covered by their family policy, and this also is a positive move, Lichter says.

The bill's focus on prevention and wellness will benefit infectious disease and public health initiatives.

"There are a few things in the bill that we're pleased to see stay in the final version," says **Michael Ochs**, government relations associate with the Infectious Diseases Society of America (IDSA) in Arlington, VA.

The bill's emphasis on wellness and disease prevention with billions of additional federal dollars for these is one example, Ochs says.

The bill's impact on physician and other provider payments is a more mixed bag, however. *(See story on*

physician payments, below.)

"There's a 10% incentive pay for primary care and general surgery," says **Jason A. Scull**, program officer for clinical affairs at IDSA.

"They're focusing on primary care in a lot of these new innovative payment models, but I think primary care does need to be incentivized," Scull says.

But the drawback is that cognitive specialists, like infectious disease specialists, cardiologists, and neurologists, could be shortchanged as the pie is cut differently, but not expanded.

"There will be unintended consequences," Scull notes. "Already last year the Centers for Medicare & Medicaid Services [CMS] eliminated payments for consultation codes that cognitive specialties use to give them money to distribute elsewhere in the fee schedule and to send more to primary care physicians."

This redistribution of payments might result in fewer medical students choosing to spend extra years of training beyond their general internal medicine residency, he adds.

While the sweeping health care reform provides some specifics on how changes will occur in the industry, no one knows precisely how things will change until the regulatory details emerge, the experts say.

"There are a lot of moving pieces to this," Scull says. "I think it's anybody's guess to where all of this ends up."

Doctors will be more closely scrutinized with bill's provisions

Experts talk about bill's negatives

PAY ATTENTION TO THE NEW HEALTH CARE BILL'S REGulatory details, experts warn providers.

There are some items in the sweeping legislation that could result in more documentation, work, and risk for physicians and other providers.

For instance, the new bill makes it clear that the government wants doctors to be doctors and not own hospitals, says **LaDale K. George**, JD, a partner with Neal, Gerber, Eisenberg in Chicago, IL.

The bill puts a moratorium on any physician-owned hospitals in non-rural settings that were not Medicare providers as of December 2010.

"The new law says that the practice of physicians owning hospitals no longer is allowed," he explains. "If a physician owns or has a financial interest in a hospital and refers patients to that hospital then every service the patient receives at the hospital is a Stark violation of $25,000 per incident."

Also, the anti-kickback law has been changed by the new bill.

"The way the new act changes it is that it appears to eliminate the need to have actual knowledge or specific intent to violate the statute," George says. "It moves in the direction of where the Stark law is where if you do not meet the safe harbors in which providers can refer to one another and engage in commercial practices together then you will be viewed as being guilty."

From physicians' perspectives, some of the other requirements will be more onerous, particularly as far as documentation and accounting are concerned.

For instance, the bill's Physician Payment Sunshine Provision requires physicians to disclose every payment they receive from pharmaceutical and biotech companies in excess of $100, and this includes drug samples. This could prove to be an accounting problem for physician investigators and others.

This likely will be a headache to physicians, who will have to keep track of every sample they receive and every payment that flows through to them for research, George says.

The new health care bill also appears to give physicians incentives and/or penalties depending on their compliance with reporting data as part of the physician quality reporting initiative (PQRI), which was established with the 2006 Tax Relief and Health Care Act.

"What's clear is that Congress is moving into the direction of mandating physicians to participate in PQRI and also moving in the direction of mandating physician resource use reporting," says **Jason A. Scull**, program officer for clinical affairs at the Infectious Diseases Society of America.

"These are somehow merged into a value modifier that also will adjust payment based on the quality of care they provide," Scull says.

About one of six eligible physicians now makes the reports, and about half of these receive incentive payments, he adds.

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 15, NUMBER 5 PAGES 9-10 MAY 2010

Statins and risk of developing diabetes

Source: Sattar N, et al. Statins and risk of incident diabetes. *Lancet* 2010;375: 735-742.

THERE IS LITTLE DISPUTE REGARDING THE beneficial reduction in CV events seen with statin treatment of dyslipidemic patients. At the same time, however, conflicting evidence has suggested that statin treatment might be associated with an increased risk of new-onset diabetes.

Sattar et al performed a meta-analysis of data from large statin clinical trials (n = 13), totalling almost 100,000 patients. During a mean follow-up of 4 years, 9% more individuals developed new diabetes on a statin than patients not treated with a statin. Since CV risk reduction was still favorably influenced by statin treatment, this small increase incidence of diabetes was either not sufficient to offset other beneficial vascular effects, or, once diabetes developed, statin protection was already on board, or perhaps both factors were influential.

You may recall that in hypertension treatment trials, a similar problem has been identified. Chlorthalidone (ALLHAT) had a significantly greater risk for incidence of new diabetes than comparators, yet this adverse effect did not seem to adversely affect CV event rates.

The mechanism by which statins increase risk for diabetes is obscure. This data analysis calculated that 255 subjects would have to be treated with a statin for 4 years to incur 1 additional new case of diabetes. Fortunately, if the small increase is real, it is strongly counterbalanced by well-documented reductions in CV events.

Maximize benefits of metform in DM2

Source: Brown JB, et al. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care* 2010;33:501-506.

TO DATE, CONTROLLED TRIALS INDICATE THAT no matter what pharmacotherapy is used to control glucose in type 2 diabetes (DM2), one can anticpate a progressive loss of control over time. Loss of efficacy is termed secondary failure: An initially effective medication later becomes insufficient to maintain control. It seems to me that this is too harsh an indictment of pharmacotherapy, since even if the medication continues with similar action over long time periods, confounders such as weight gain, inherent disease progression, and addition of confounding comorbidities might make it appear as if the medication is failing, when in reality, counterbalancing forces are increasing.

In any case, Brown et al performed an observational cohort study of DM2 subjects (n = 1799) initially treated with metformin monotherapy successfully (i.e., able to maintain an A1c < 7.0 without adding a second agent). Secondary failure was defined as either the addition of a second agent, or an increase of A1c above 7.0 while still on monotherapy. Subjects who required additional therapy within the first 6 months of metformin treatment were regarded as primary failure, and were excluded from this analysis.

In subjects able to maintain good control with initial metformin monotherapy, secondary failure occurred at a rate of 17% per year. Predictors of higher failure rates included longer duration of diabetes before treatment and higher baseline A1c at initiation of treatment. These data suggest that early initiation of treatment, especially when A1c is not yet markedly elevated, results in greater durability of metformin efficacy.

Prediabetes therapy and beta-cell function

Source: Hanley AJ, et al. Effect of rosiglitazone and ramipril on {beta}-cell function in people with impaired glucose tolerance or impaired fasting glucose. *Diabetes Care* 2010;33:608-613.

PREDIABETES (PDM) IS DEFINED AS EITHER impaired fasting glucose (FBG = 100-125 mg/dL), impaired glucose tolerance (IGT; 2-hour post-load glucose = 140-199 mg/dL), or supranormal but not diabetic A1c (A1c = 5.7-6.4). Untreated pDM predictably progresses to frank DM at a rate of about 7%-10% per year. Numerous interventions have been shown to alter the progression from pDM to diabetes, including diet, exercise, metformin, acarbose, orlistat, and thiazolidinediones; this year, nateglinide, an insulin secretagogue, was not confirmed to delay progression from pDM to diabetes.

Hopefully, treatments to prevent diabetes will also impact beta-cell function favorably, rather than simply compensate for progressive metabolic decline. The DREAM trial (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) randomized 5269 pDM subjects to ramipril and/or rosigliatoze. A substudy of DREAM (n = 982) had measurements of beta-cell function at baseline and periodically during the 3-year (median) follow-up, as well as measurements of progression from pDM to DM.

Subjects randomized to ramipril did not experience any meaningful change

in beta-cell function. In contrast, rosiglitazone-treated subjects enjoyed substantial improvements in beta-cell function. Benefits were less in pDM subjects who only manifest IFG compared with IGT or both.

In addition to reducing beta cells induced by glucotoxicity, thiazolidinediones lower free fatty acid levels, which may favorably affect beta-cell apoptosis.

Onychomycosis: Long-term follow-up

Source: Piraccini BM, et al. Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. *J Am Acad Dermatol* 2010;62:411-414.

Although onychomycosis (ONCM) is often considered a cosmetic problem, some patients suffer significant disability due to foot pain, and difficulty wearing shoes. The treatment course for toenail ONCM is lengthy and costly. There are few data on long-term follow-up to ascertain recurrence rates, although prevailing opinion suggests recurrence is common.

Praccini et al performed a prospective study of ONCM patients (n = 73) who had been treated with pulse therapy (treatment 1 week/month for 6 months) with terbinafine or itraconazole. After clinical cure, subjects were prospectively followed for 7 years. Cure was defined as normalized clinical appearance and negative fungus culture.

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Patients were seen every 6 months during follow-up. Overall, recurrence developed in 16.4% of subjects. Each case of recurrence involved the same organism identified in the original infection. However, the recurrence rate for itraconazole was 3-fold greater than terbinafine. Terbinafine is widely regarded as the treatment of choice for toenail ONCM; this trial suggests superior durability of cure for terbinafine when compared with itraconazole.

Diagnostic yield of elective coronary angiography

Source: Patel MR, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886-895.

Current recommendations suggest that in stable persons under consideration for CAD evaluation, low-risk individuals be observed, high-risk patients be triaged to coronary angiography, and intermediate-risk persons be further stratified by means of non-invasive testing. Such guidance is structured to minimize unnecessary invasive investigations in low-risk individuals, and to identify — in the group of intermediate risk — those who merit follow-up with angiography.

The American College of Cardiology National Cardiovascular Data Registry provided information on patients without known CAD (n = 398,978) who received coronary angiography (electively) at hospitals in the United States during a 4-year interval commencing January, 2004.

Obstructive CAD was defined as at least 50% stenosis of the left main coronary artery (or greater degrees of stenosis of epicardial vessels). Catheterization determined that slightly more than one-third of patients had obstructive CAD. In addition to the disappointingly low percentage of individuals identified with CAD on angiography, this study also provided insights about the concordance of risk and use of non-invasive testing (i.e., stress testing). When non-invasive testing had preceded angiography, subjects' baseline risk category was at odds with the current recommendations focusing upon refinement of risk in persons at intermediate Framingham scores, in that those with high Framingham risk scores were disproportionately represented. The authors suggest that the diagnostic yield based upon current practice needs improvement.

Thyroid hormone analogue for dyslipidemia

Source: Ladenson PW, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N Engl J Med* 2010;362:906-916.

The role of statins in treatment of dyslipidemia is well established. There are, however, limitations of statins: Residual risk is substantial, not all persons can tolerate statins, and, even with full-dose statin treatment, some patients do not achieve lipid goals.

The role of the thyroid in lipid metabolism has long been a matter of scientific interest. It is recommended that patients with dyslipidemia undergo thyroid function testing since hypothyroidism, although only present in a small percentage of dyslipidemic patients, is readily correctible and offers meaningful lipid improvements. Enhancement of thyroid activity has favorable lipid effects. As far back as the 1960s, investigators were curious enough about thyroid hormone and vascular disease to enroll men in the Coronary Drug Project (1965) and randomize them to d-thyroxine, which was felt at the time (mistakenly) to have essentially no effect on sympathetic nervous system sensitivity, but favorable effects on lipids.

Eprotirome (EPR) is an analogue of thyroid homone which has preferential affinity for thyroid receptors that modulate lipid lowering, as compared to cardiac receptors. A randomized placebo-controlled, double-blind study was done among patients on an NCEP step 1 diet and a statin (simvastatin or atorvastatin). Patients (n = 329) received statin plus either EPR or placebo for 12 weeks.

At the end of the trial, very favorable lipid effects were reported with the addition of EPR to a statin: a 22%-32% reduction in LDL, a 6- to 9-fold increase in patients achieving an LDL < 100 mg/dL, as well as favorable effects on triglycerides and apoB (all dose-dependent). A small reduction in HDL was seen. There was no change in heart rate or BP. Selective activation of thyroid receptors may one day provide an additional path for successful lipid modulation.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Finding ACCORD in the Management of Type 2 Diabetes?

In this issue: Examining the three arms of the ACCORD trial; and FDA Actions: clopidogrel, dexlansoprazole, and tamsulosin.

ACCORD and type 2 diabetes

Every once in a while a medical study comes along that turns medical dogma on its ear. The Multiple Risk Factor Intervention Trial (MRFIT), published in 1982, was such a study, so was the Women's Health Initiative (WHI), published in 2002. Both studies challenged conventional wisdom and changed practice. MRFIT caused us to take a hard look at risk factor intervention especially hypertensive treatment, while WHI established that combination hormone therapy in postmenopausal women should no longer be routinely recommended because of the risk of breast cancer and heart disease.

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial, published in March in the *New England Journal of Medicine*, is also such a study, and is destined to change medical practice in the treatment of type 2 diabetes. ACCORD looked at three aspects of care in type 2 diabetes, the first was the effects of intensive glucose lowering, the second was the effect of intensive blood pressure control, and the third was the effect of combination lipid therapy.

The intensive glucose lowering study was published early in 2008 when it was found that the intensive therapy group (targeting hemoglobin A1c < 6.0%) reported a higher mortality than the standard therapy group (targeting A1c 7.0%-7.9%). At the same time, intensive therapy did not significantly reduce major cardiovascular events (*N Engl J Med* 2008;358:2545-2559).

The second and third wings of the ACCORD trial were published on-line March 14, and the results were similarly discouraging for aggressive care. A total of 4733 participants with type 2 diabetes were enrolled in the intensive blood pressure control wing and were randomized to intensive therapy, targeting a systolic pressure < 120 mmHg, or standard therapy targeting a systolic blood pressure < 140 mmHg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, mean target blood pressures were met in both groups. The annual rate of the primary outcome was 1.87% in the intensive therapy group and 2.09% in the standard therapy group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.73-1.06; P = 0.20). The annual rates of death from any cause were 1.28% in the intensive therapy group and 1.19% in the standard therapy group (HR, 1.07; 95% CI, 0.85-1.35; P = 0.55). There was a slightly reduced risk of stroke in the intensive therapy group (0.32% vs 0.53%; P = 0.01); however, serious adverse events were more than double in the intensive therapy group. The authors conclude

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

that in patients with type 2 diabetes targeting systolic blood pressure < 120 mm Hg as compared to < 140 mm Hg did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events (*N Engl J Med* published on-line March 14, 2010). While these results are somewhat surprising, they may not change the general recommendation for more aggressive blood pressure management in type 2 diabetes to systolic blood pressure ≤ 130/80 mm Hg, which is consistent with most current guidelines (including JNC VII).

In the third wing of ACCORD, 5518 patients with type 2 diabetes who were being treated with the statin simvastatin were randomized also to receive fenofibrate or placebo. The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, the annual rate of primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR 0.92; 95% CI, 0.79-1.08; P = 0.32). There were also no significant differences between the two study groups with respect to any secondary outcomes or death rate. Subgroup analysis suggested slightly higher benefit for men vs women and perhaps a benefit for those with high baseline triglycerides (> 204 mg/dL) and low HDL (≤ 34 mg/dL). The authors conclude that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone (*N Engl J Med* published on-line March 14, 2010). This study does not in any way diminish the known benefit from aggressive statin therapy in type 2 diabetics, but does suggest that targeted treatment of triglycerides with fenofibrate is of no value. The FDA is reviewing the ACCORD data, but as of this time they have "made no new conclusions or recommendations regarding the use of simvastatin or other statin drugs and fenofibrate."

Do statins increase the risk of type 2 diabetes? It has been suggested that lipophilic statins may cause unfavorable metabolic side effects such as reduction of insulin secretion and worsening of insulin resistance. In a small single-blind, placebo-controlled parallel study, 40 to 44 patients were randomized to receive placebo, or atorvastatin 10, 20, 40, and 80 mg during a 2-month period. While atorvastatin significantly reduced LDL and apolipoprotein B levels, the drug was also associated with significantly increased fasting plasma insulin levels, as well as hemoglobin A1c levels (mean changes in fasting insulin levels, 25%, 42%, 31%, and 45%, respectively, for increasing dose; A1c increases of 2%, 5%, 5%, and 5%, respectively; P < 0.05 by paired t-test). Atorvastatin also decreased insulin sensitivity in a dose-responsive fashion. The authors conclude that atorvastatin resulted in significant increases in fasting insulin, hemoglobin A1c consistent with increased insulin resistance (*J Am Coll Cardiol* 2010;55:1209-1216). Previous studies have shown similar results with lipophilic statins including atorvastatin, rosuvastatin, and simvastatin, while pravastatin seems to reduce the risk of diabetes.

FDA Actions

The FDA has issued a warning to health care providers regarding the antiplatelet drug clopidogrel (Plavix®). It is recently been found that up to 14% of the population did not metabolize the drug effectively and may not fully convert the drug to its active form. Clopidogrel is dependent on CYP2C19 and those that genetically lack the enzyme may not convert the drug to its active form. Recent studies have suggested that reduced CYP2C19 activity was associated with higher risk for cardiovascular outcomes. A test is available to identify genetic differences in CYP2C19 function and the FDA is recommending that health care professionals consider use of other antiplatelet medications or use alternative dosing if patients are poor metabolizers. The manufacturer of Plavix is being asked to add a black box warning to the drug labeling to this effect. Previously, it was discovered that some proton pump inhibitors including omeprazole may also inhibit metabolism to the active drug. Meanwhile Eli Lilly's prasugrel (Effient®), a direct competitor to clopidogrel, is not affected by CYP genetic variants.

The FDA has approved Takeda Pharmaceutical's request to change the name of its proton pump inhibitor dexlansoprazole from Kapidex® to Dexilant™. The change is being made due to several dispensing errors that occurred between Kapidex and the prostate cancer drug Casodex® (bicalutamide) and the analgesic Kadian® (morphine).

The FDA has approved a generic version of Boeringer Ingelheim's tamsulosin (Flomax®) for the treatment of benign prostatic hyperplasia in men. Generic tamsulosin should be available later in 2010.