INTERNAL MEDICINE ALERT

Providing Evidence-based Clinical Information for 30 Years

A twice-monthly update of developments in internal and family medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Financial Disclosure:
Internal Medicine Alert's editor, Stephen Brunton, MD, serves on the advisory board for Lilly, Boehringer Ingelheim, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Lilly, Kowa, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Muscle Complications Due to Statins

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor, Clinical Neurology, Weill Cornell Medical College

This article originally appeared in the February issue of Neurology Alert. *At that time it was peer reviewed by M. Flint Beal, MD, Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center, New York, NY. Dr. Rubin and Dr. Beal report no financial relationships relevant to this field of study.*

Synopsis: *A small percentage of patients taking statins may develop muscle symptoms (pain and weakness) but elevated CK is rare.*

Source: El-Salem, K, et al. Prevalence and risk factors of muscle complications secondary to statins. *Muscle Nerve* 2011;44:877-881.

WHICH RISK FACTORS PREDISPOSE PATIENTS TO MUSCLE COMPLICATIONS from statin therapy? At King Abdullah University Hospital (KAUH), Irbid, Jordan, 345 consecutive patients receiving statins were enrolled during a 12-month period into a prospective comparative study. Subjects were compared to 85 age- and sex-matched controls to determine the prevalence and risk factors of statin-associated muscle complications. Neurological symptoms predating statin therapy were analyzed carefully to distinguish them from those beginning after statin administration. Controls were recruited from the general medicine and neurology clinics of KAUH, were not on statins, and were usually seen for headaches. Statistical analysis encompassed Chi-square and independent-sample t-tests, included calculation of crude odds ratios and their 95% confidence intervals, with $P < 0.05$ considered statistically significant.

Among 345 statin-treated patients (207 men and 138 women; mean age of 57 years), muscle symptoms were reported in 21%, compared to 5.9% of controls, and included muscle pain, tenderness, fatigue, weakness, stiffness, or cramps ($P = 0.0013$). Statins used included atorvastatin (n = 219), simvastatin (n = 58), fluvastatin (n = 47), pravastatin (n = 19), and rosuvastatin (n = 7). Weakness, always mild

VOLUME 34 • NUMBER 4 • FEBRUARY 29, 2012 • PAGES 25-32

INTERNAL MEDICINE ALERT IS AVAILABLE ONLINE
www.internalmedicinealert.com

(4+ on MRC scale), usually bilateral in both arms and legs, and proximal more than distal, was found on examination in 15% of those who reported muscle symptoms, approximately 3.2% of the total group, but was not found in any patient who denied muscle symptoms, nor in any control. Elevated creatine kinase (CK), three to fourfold normal, was seen in only two patients, both of whom had both muscle symptoms and weakness, and both of whom also were taking fibrates. Elevated CK was not seen in any patient with symptoms alone, without clinical weakness. Age over 60 years, greater than 10-month statin usage, a history of diabetes or stroke, and lower body mass index all were associated with a statistically significant increased risk of developing muscle-related symptoms. Statin dose, gender, thyroid, liver, kidney, and cardiovascular disease did not correlate with symptom development. Specific patient and disease characteristics appear to associate with adverse reactions to statins.

■ COMMENTARY

Although the precise mechanism of statin-induced myopathy remains uncertain, multiple mechanisms have been proposed. Depletion of isoprenoids, the lipid byproducts of the HMG-CoA reductase pathway, may reduce protein prenylation, which negatively affects small GTPases and lamins, causing vacuolization of muscle fibers, organelle swelling and degeneration, and apoptosis. Statins may inhibit ubiquinone or coenzyme Q10 synthesis, which would interfere with mitochondrial respiratory chain function and energy production. Impaired calcium metabolism may open ryanodine receptors resulting in greatly increased intracellular calcium. Autoimmune pathways are implicated as statins activate T lymphocytes and appear to upregulate MHC-1 expression. Sarcolemmal cholesterol reduction may destabilize the membrane by altering membrane fluidity and integrity.[1] Mice studies suggest that protection from statin complications may be obtained by an exercise program prior to statin initiation.[2] What can be done once statin myopathy is evident? Options include switching to another statin at a lower dose, using longer acting statins (including rosuvastatin and atorvastatin), and switching to non-statin lipid-lowering agents. ■

References

1. Abd TT, Jacobson TA. Statin-induced myopathy: A review and update. *Expert Opin Drug Saf* 2011;10: 373-387.
2. Meador BM, Huey KA. Statin-associated changes in skeletal muscle function and stress response after novel or accustomed exercise. *Muscle Nerve* 2011;44:882-889.

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, a division of Thompson Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie Coplin.
SENIOR MANAGING EDITOR: Neill L. Kimball.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $21.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: neill.kimball@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 45 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This Enduring Material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for up to 24 Prescribed credits by the American Academy of Family Physicians. AAFP accreditation begins 01/15/12. Term of approval is for 1 year from this date. Each issue is approved for 1 Prescribed credit. Credit may be claimed for 1 year from the date of each issue. The AAFP invites comments on any activity that has been approved for AAFP CME credit. Please forward your comments on the quality of this activity to cmecomment@aafp.org.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

AHC Media

Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

Optimal Weight Loss Diet to Reduce Cardiovascular Risk

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Professor of Medicine, University of California, San Francisco, Chief of Clinical Cardiology, University of California, San Francisco Medical Center, Editor for Clinical Cardiology Alert

This article originally appeared in the February issue of Clinical Cardiology Alert. *At that time it was peer reviewed by Ethan Weiss, MD, Associate Professor of Medicine, Division of Cardiology, University of California, San Francisco, CA. Dr. Weiss is an advisory board member for Bionovo. Dr. Crawford reports no financial relationships relevant to this field of study.*

Synopsis: *The authors conclude that after weight loss, a low glycemic index and, to a lesser extent, low-protein diet may reduce inflammation associated with cardiovascular disease in overweight adults.*

Source: Gogebakan O, et al. Effects of weight loss and long-term maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: The Diet, Obesity, and Genes (DiOGenes) study: A randomized controlled trial. *Circulation* 2011;124:2829-2838.

This pan-European multicultural study investigates whether after initial weight loss in overweight subjects, a subsequent diet of high or low carbohydrate (gly-

cemic index) or protein diets helped subjects maintain their new weight better. Their initial results showed that the low glycemic, high-protein diet was superior for maintaining their weight for 26 weeks. The present study evaluated which diet best improved hsCRP, triglycerides, cholesterol levels, and blood pressure vs a control group in 932 overweight adults who lost weight on an 8-week low-calorie diet. Of the 773 randomized to one of the four diets, 71% completed the study. Average weight loss in the low-calorie period was 11 kg. Of the subsequent diets, only the low-protein high-glycemic diet resulted in weight regain (+ 1.7 kg). Weight loss reduced hsCRP, cholesterol (HDL and LDL), triglycerides, and blood pressure. During the maintenance phase, hsCRP was reduced further in the low-glycemic diets vs high and on low protein diets vs high. Cholesterol, triglycerides, and blood pressure were not differentially affected by the four diets. The authors conclude that after weight loss, a low glycemic index and, to a lesser extent, low-protein diet may reduce inflammation associated with cardiovascular disease in overweight adults.

■ COMMENTARY

With two-thirds of American adults being either overweight or obese, scientific data on appropriate diets are important. The original trial report of this study showed that caloric restriction was necessary for weight loss and diet composition had little effect. The emphasis on low-fat diets to reduce cholesterol and reduce cardiovascular risk may be thwarted if subjects substitute carbohydrates for the fat calories, resulting in little or no weight loss. As this follow-up study shows, a high glycemic index diet may also blunt the decrease in low-grade inflammation associated with weight loss and increase cardiovascular risk. Maintaining a high-protein diet also can blunt the decrease in hsCRP following weight loss, but to a much lesser extent than a high-glycemic diet. However, high-protein diets are known to improve lipid profiles. What the balance between lower LDL cholesterol and higher inflammation will do to subsequent cardiovascular risk is not known, but since cholesterol can be lowered by other means, the lower inflammation on a low-glycemic diet could be more important. In summary, this study argues for adopting low glycemic index diets with lower protein content for weight loss and maintenance.

The strengths of this study are that the subjects were otherwise healthy without diabetes, morbid obesity, and other chronic diseases. Also, the study separated the effects of weight loss from the effects of dietary composition. However, it must be emphasized that the effects of weight loss on all the metabolic, inflammatory, and blood pressure measures was greater than the effects of dietary composition. ■

Sweat Your Heart? Sauna for CHF

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Clinical Assistant Professor, School of Medicine, University of North Carolina, Chapel Hill, NC, Visiting Assistant Professor, University of Arizona, College of Medicine, Tucson, AZ, Editor for Alternative Medicine Alert

This article originally appeared in the February issue of Alternative Medicine Alert. *At that time it was peer reviewed by David Kiefer, MD, Clinical Instructor, Family Medicine, University of Washington, Seattle, Clinical Assistant Professor of Medicine, University of Arizona, Tucson, Adjunct Faculty, Bastyr University, Seattle. Dr. Greenfield and Dr. Kiefer report no financial relationships relevant to this field of study.*

Synopsis: *The prevalence of chronic heart failure has steadily increased with improvements in survival rates for cardiac patients; however, heart failure remains a disorder whose typically progressive course worsens quality of life, and thus far has defied most conventional medical approaches. New ideas leading to new treatments are needed. The researchers behind this small intervention trial examined the effect of repeated sauna therapy on exercise tolerance in people with congestive heart failure — and found significant benefits.*

Source: Ohori T, et al. Effect of repeated sauna treatment on exercise tolerance and endothelial function in patients with chronic heart failure. *Am J Cardiol* 2012;109:100-104.

THE RESEARCHERS BEHIND THIS CLINICAL INTERVENTION trial sought to assess the impact of Waon therapy (repeated sauna therapy) on exercise tolerance in people with congestive heart failure (CHF). Subjects had to have stable, compensated NYHA functional class II heart failure and/or previous hospitalization for worsening failure to be included in the trial; a total of 41 subjects entered into the protocol (mean age 68 years). Participants underwent Waon therapy with a far-infrared dry sauna (temperature maintained at 60° C) daily on weekdays for 3 weeks (n = 15 sessions) while continuing to receive conventional medical care for CHF. Treatment consisted of the subjects initially sitting in the sauna for 15 minutes, followed by bed rest for 30 minutes while covered with a blanket to maintain warmth. Assessments completed before and after the 3 weeks of intervention included body weight, 6-minute walk distance (6MWD), cardiopulmonary exercise testing in those physically able to pump the pedals of an ergometer (n = 20), and symptom-limited cardiopulmonary exercise testing using expired gas analysis. Vascular endothelial function was evaluated through determination

of flow-mediated dilation (FMD) of the brachial artery. Echocardiography was performed, as was measurement of neurohumoral factors and the number of circulating CD34+ cells. Subjects were weighed before and after the therapy and drank water to compensate for the weight loss.

By the end of the 3-week study significant improvements with Waon therapy had been identified, including an increase in left ventricular ejection fraction from 30.4% to 32.5% ($P = 0.023$), an improvement in peak oxygen uptake, slight improvement in left ventricular ejection fraction, a reduction in plasma norepinephrine levels from 400 to 300 pg/mL ($P = 0.015$), a decrease in brain natriuretic peptide from 550-416 pg/mL ($P = 0.035$), improvement in FMD from 3.5%-5.5% ($P < 0.001$), and an increase in 6MWD from 337-379 m ($P < 0.001$). There was also an increase in the number of circulating CD34+ cells ($P = 0.025$). A multivariate analysis revealed that change in FMD was the only independent determinant of change in 6MWD. Findings did not vary according to severity of heart failure or subject age.

The authors concluded that repeated sauna therapy in people with chronic heart failure may improve exercise tolerance in association with improvement in endothelial function.

■ COMMENTARY

The findings from this small study are startling, though perhaps they shouldn't be, as the researchers reference five prior studies suggesting that significant cardiovascular benefits could be expected from repeated sauna therapy. Compelling, however, are the conclusions that three weeks of Waon therapy in people with CHF not only improves exercise tolerance and ejection fraction, but also curtails neurohumoral activation and enhances endothelial function; this in the setting of a disease whose progression typically is deemed inexorable, in large part due to persistent deterioration in endothelial and cardiac function associated with neurohumoral activation and cardiac remodeling. The theory currently holding sway regarding potential mechanistic actions of Waon therapy and its cardiovascular health benefits is that such treatment may increase nitric oxide bioavailability, thus creating a direct benefit to endothelial function, but not a direct impact on cardiac function.

There is at least one other interesting finding noted by the study authors, that being the effect of Waon therapy on the number of circulating CD34+ cells. These cells are considered to be precursors of endothelial progenitor cells (EPCs), which since being identified in the late 1990s have been used alternately as biomarkers for cardiovascular disease or actual angiogenic therapies that might promote repair of damaged vascular endothelium.[1] This therapeutic approach is in its relative infancy, but interest in it has spawned a large number of research studies in recent years.

It is important to keep in mind that the current study has major limitations, not the least of which are the small sample size, the brief duration of treatment, the lack of a control group, and the short follow-up period. Nonetheless, findings such as these have the potential to leave us with a sense of wonder in the face of complex issues such as heart failure — could it be that a straightforward, inexpensive treatment that raises core body temperature by 1.0-1.2° C is sufficient to help improve cardiovascular fitness in people with CHF? It is too early to say, but there is ample reason for excitement as we await the findings of future studies on the topic that must surely be forthcoming. Sometimes the simple, elegant approach to problems yields important answers — it would be good news for those experiencing CHF, indeed, if such were the case here. ■

Reference

1. Siddique A, et al. Endothelial progenitor cells: What use for the cardiologist? *J Angiogen Res* 2010;2:6. Doi: 10.1186/2040-2384-2-6.

Solvents and the Risk of Parkinson's Disease

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Associate Professor, Neurology and Neuroscience, Weill Cornell Medical College

This article originally appeared in the February issue of Neurology Alert. *At that time it was peer reviewed by M. Flint Beal, MD, Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center, New York, NY. Dr. Nirenberg and Dr. Beal report no financial relationships relevant to this field of study.*

Synopsis: *Exposure to specific solvents, and trichloroethylene in particular, is associated with an increased risk of Parkinson's disease.*

Source: Goldman SM, et al. Solvent exposure and Parkinson disease risk in twins. *Ann Neurol* 2011; DOI:10.1002/ana.22629.

PARKINSON'S DISEASE (PD) HAS BEEN CLOSELY LINKED TO both genetic and environmental factors. In prior studies, environmental exposures associated with PD have included pesticides, well water consumption, and residency in rural areas; inverse risk factors have included smoking and coffee use. Some studies have implicated solvents in PD risk, but data have been lacking about whether (and which) solvents may be involved.

In this study, the authors examined the potential association between PD and exposure to six specific solvents. They used a case-control study design, with 99 pairs of twins who were discordant for PD status. Study subjects, all of whom were male, were recruited from the National Academy of Sciences/National Research Council World War II Veteran Twins Cohort. Structured questionnaires were used to obtain detailed lifetime occupational and hobby histories from each subject. Expert raters, blinded to PD status, then used this information to infer each subject's lifetime exposure to these six solvents.

The authors found that ever exposure to trichloroethylene (TCE) was associated with an increased risk of PD (odds ratio [OR], 6.1; $P = 0.034$). There also were non-significant trends toward increased PD risk with ever exposure to perchloroethylene (PERC; OR, 10.5; $P = 0.053$) or carbon tetrachloride (CCl4; OR, 2.3; $P = 0.088$). There were similar findings when they examined the duration of exposure and cumulative lifetime exposure to these solvents. Based on these findings, the authors conclude that solvents, and TCE in specific, are associated with an increased risk of PD.

■ COMMENTARY

In this small but well-designed epidemiological study, the authors provide new evidence to support the association between solvent exposure and PD, with a significant association between PD and TCE, and similar trends for PERC and CCl4. Given that these solvents are commonly used in industry, dry cleaning, and household products, the findings have major public safety implications.

Study strengths include the population-based study design and use of twin pairs to minimize potential confounders. Limitations include the small sample size, retrospective study design, and inferred calculation of solvent exposure. In addition, the study sample consisted exclusively of male World War II veterans, such that the results may not be generalizable to other populations.

In summary, this study suggests that exposure to specific solvents may increase the risk of PD. Given the major public health implications of these findings, further studies in larger, prospective cohorts are warranted. ■

Care Options for Breast Cancer Survivors

ILLUSTRATIVE CASE SERIES

By Jerome W. Yates, MD

Professor of Medicine, SUNY at Buffalo; Professor of Oncology, Roswell Park Cancer Institute, Buffalo, NY;

Senior Clinical Research Scientist, Clinical Research Branch, NIA, NIH

This article originally appeared in the February issue of Clinical Oncology Alert. *At that time it was peer reviewed by V.R. Veerapalli, MD, Staff Clinician, INOVA Fairfax Cancer Center, Falls Church, VA. Dr. Yates and Dr. Veerapalli report no financial relationships relevant to this field of study.*

A 57-YEAR-OLD POSTMENOPAUSAL LIBRARIAN, WHO is 1-year post diagnosis of a stage II invasive cancer of the right breast, is found to be estrogen- and progesterone-receptor positive, and Her2neu negative with one positive axillary node. Following the completion of breast conserving tumor resection, adjuvant chemotherapy, and radiation treatment, she was given the option of being followed by her surgeon, medical oncologist, radiation therapist, primary care physician, or a nurse practitioner in the multidisciplinary clinic. She was not comfortable with the consultant medical oncologist and was favorably inclined toward the nurse practitioner, having been assured that she would see her at each follow-up visit. Her previous primary care physician retired during the course of her adjuvant chemotherapy. She elected to be followed by telephone conversations with a nurse practitioner and customary repeated mammograms.

■ CASE DISCUSSION

A recent paper using a survey methodology to explore various follow-up options for breast cancer survivors examined patient comfort with providers "most likely to decrease worry and increase survival."[1] Included options were being seen by a medical oncologist, surgeon, radiation oncologist, nurse practitioner, primary care physician, or a virtual visit using either a telephone or internet interaction. This study included 218 breast cancer survivors and reaffirmed some of our knowledge about provider-patient relationships. Those surveyed favored follow-up visits from medical oncologists over the other options. They also favored being followed by their primary care physicians over nurse practitioners and were least interested in virtual visits. The authors note that other investigators found that psychosocial support for patients with cancer had been effectively provided through periodic telephone-based follow-up.[2] Another study demonstrated that telephone conversations with trained nurses as opposed to appointments with specialists failed to demonstrate differences in patient satisfaction, anxiety, or the detection of recurrences.[3]

Although the results of this study appear consistent with most expectations, it has serious limitations. The survey inclusion rate was only 40% in what would normally be a highly motivated cancer population. The respondents were significantly younger than the overall population, were highly educated with 71% having completed college, and 51% had an annual household income of greater than $80,000. It could be expected that in the future, highly educated patients might be more receptive to virtual visits as

was the case for the librarian mentioned above. However, in this study, technological expertise did not overcome survivor interest in direct interactions with their providers.

Was the librarian's selection of telephonic follow-up rational or merely based on her discomfort with the medical oncologist responsible for her adjuvant care and the loss of her primary care physician to retirement? As a trained librarian she was comfortable with electronic support services and perhaps more knowledgeable than others confronted with the selection of their survival management. In an effort to better understand why she would select the least personal interaction for her follow-up, some understanding of patient comfort and trust in caregivers deserves exploration.

Multiple factors contribute to patient confidence in their providers, and these include the following: trust in their provider to act in their best interests, their perception of the education and knowledge of the provider, the respect they derive from a patient-focused interaction, and their comfort with the personality and level of interest from the provider.[4] Trust is generally more likely the result of interactions with individual providers, while distrust is often associated with impersonal institutional providers.[5] This is true because the behavior of an individual is easier to predict then the less personal associations with an impersonal institution. The high-risk probability of a recurrence of disease puts the survivors in a vulnerable situation because of their inability to exercise medical control without their dependence on their knowledgeable health care provider. Patient satisfaction is based on past experiences, while confidence in providers is based on future expectations. This librarian had her confidence in the medical oncologist eroded because of past interactions. Lack of confidence translates into a lack of trust.

Provider characteristics that are important to patients include familiarity with their medical and social situation, the amount of time they spend with the patients, the information they provide, and their level of empathy in difficult situations. Patient characteristics that help providers relate favorably include loyalty, ethnicity, satisfaction, adherence to medical recommendations, and a willingness to participate in clinical trials.[4] When patients with cancer entrust their future survival to providers, it is easy to understand why they expect positive interactions with trusted providers. It is also predictable that the results of the survey would reflect the importance of personal interactions with knowledgeable, compassionate, and trusted providers. The impersonal imposition of institutional solutions (clinics, telephone, or Internet support) to solve the shortages of oncologists, primary care physicians, and nurse specialists likely will result in less patient and provider satisfaction in the future. The availability of telephonic follow-up and web-based survivorship planning and general responses to questions may benefit some patients and their families, but it also may introduce confusion and misinterpretation for the most vulnerable patients. There also will be an increase in legal liability for the provider institution. The librarian elected to take control of the situation herself because of her comfort with technological answers and her mistrust or lack of empathy from her medical oncologist. ■

References

1. Mayer EL, et al. Breast cancer survivors' perceptions of survivorship care options. *J Clin Oncol* 2012;30:158-163.
2. Gotay CC, Bottomley A. Providing psycho-social support by telephone: What is its potential in cancer patients? *Eur J Cancer Care* (Engl) 1998;7:225-231.
3. Beaver K, et al. Comparing hospital and telephone follow-up after treatment for breast cancer: Randomised equivalence trial. *BMJ* 2009;338:a3147.
4. Hillen MA, et al. Cancer patients' trust in their physician — A review. *Psychooncology* 2011;20:227-241.
5. Hall MA, et al. Trust in the medical profession: Conceptual and measurement issues. *Health Serv Res* 2002; 37:1419-1439.

Pharmacology Update

Azilsartan Medoxomil and Chlorthalidone (Edarbyclor®)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

A NEW ANGIOTENSIN II RECEPTOR BLOCKER (ARB) AND THE thiazide diuretic, chlorthalidone, has been approved as a fixed combination for the treatment of hypertension. Azilsartan medoxomil, the prodrug of azilsartan, is a selective angiotensin II AT_1 receptor antagonist. Chlorthalidone, a thiazide diuretic, has been in use for more than 50 years. The fixed combination is marketed by Takeda Pharmaceuticals America, Inc., as Edarbyclor.

Indications

The fixed combination of azilsartan/chlorthalidone (AZL/CT) is indicated for the treatment of hypertension in patients inadequately controlled with monotherapy.[1]

Dosage

The recommended starting dose is 40/12.5 mg once daily.[1] The dose may be increased to 40/25 mg daily. The tablets may be taken without regard to meals.

AZL/CT is available as 40/12.5 and 40/25 mg.

Potential Advantages

Azilsartan 40 mg produces similar blood pressure reduction to maximum doses of olmesartan (40 mg) and valsartan (320 mg).[2-4] The fixed combination of azilsartan and chlorthalidone produces a mean change in trough blood pressure (BP) of -24 to -30 (SBP) and -14 to -17 (DBP).[4] AZL/CT 40/25 mg is statistically superior to olmesartan/HCTZ 40/25 mg.[1]

Potential Disadvantages

The incidence of dizziness was 8.9% compared to < 2% for monotherapy with each component.[1] The frequency of study discontinuation was 8.3% for AZL/CT compared to 3.2% for each component. The most common reasons were increase in serum creatinine and dizziness. The frequencies of increase in serum creatinine of 30% or higher were approximately 8% for the fixed combination compared to approximately 2% for chlorthalidone monotherapy.[5] This is a known pharmacologic effect of drugs targeting the renin-angiotensin aldosterone system.[1]

Comments

Azilsartan is similar to candesartan in terms of chemical structure as well as AT1 selectivity and receptor affinity. The antihypertensive effects of AZL/CT have been evaluated in five randomized controlled studies involving more than 3000 subjects administered AZL/CT and more than 2000 given an active comparator.[1] In an 8-week trial, 1714 subjects were randomized to six combinations of AZL (20, 40, and 80 mg) and chlorthalidone (12.5 and 25 mg), as well as five arms of monotherapy for each drug. These subjects had mean baseline SBP of 165 mmHg and DBP of 95 mmHg. Change in BP was evaluated at trough (22-24 hours post dose) as well as clinic measured BP change. The fixed combination produced significant reduction in BP compared to each component alone. The effect was observed within 1 to 2 weeks. In a 12-week comparative study, AZL/CT 40/25 was found to be statistically superior to olmesartan/HCTZ (n = 719).[1] In patients with baseline BP of 165/96 mmHg, clinic measured BP reductions were -43/-19 mmHg compared to -37/-16 mmHg. Based on clinical data, patients with a baseline blood pressure of 170/105 mmHg have an 85% chance of achieving BP < 140 SBP and < 90 DBP with AZL/CT 40/25 mg.[1]

Clinical Implications

Azilsartan is the eighth ARB to enter the market. The fixed combination appears to produce significant reduction in SBP and DBP. It may offer an option for patients with high baseline BP. ■

References

1. Edarbyclor Prescribing Information. Deerfield, IL: Takeda Pharmaceutical America, Inc; December 2011.
2. Edarbi Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc; November 2011.
3. White WB, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. *Hypertension* 2011;57:413-420.
4. Sica D, et al. Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. *J Clin Hypertens* 2011;13:467-472.
5. Zaiken K, et al. Azilsartan medoxomil: A new angiotensin receptor blocker. *Clin Ther* 2011;33:1577-1589.

CME Objectives

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

CME Questions

1. Which of the following characteristics is *NOT* associated with muscle complications from statin therapy?
   a. Diabetes
   b. Stroke
   c. Lower body mass index
   d. Liver disease
   e. Age over 60 years

2. The best diet for maintaining weight loss and enhancing cardiovascular protection is:
   a. high protein, low carbohydrates.
   b. high protein, high carbohydrates.
   c. low carbohydrates, low protein.
   d. high carbohydrates, low protein.

3. Which of the following solvents has been most closely associated with an increased risk of Parkinson's disease?
   a. n-Hexane
   b. Xylene
   c. Toluene
   d. Trichloroethylene

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Subclinical Atrial Fibrillation

Source: Healey JS, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;366:120-129.

I HAVE BEEN A STUDENT OF ATRIAL FIBRILlation (AF) for some time, but had never come upon the term "subclinical" AF until this *New England Journal of Medicine* publication. The authors point out that although AF is often brought to our attention by awareness of an arrhythmia, it is often asymptomatic — what they call subclinical. Indeed, it is not uncommon to see patients presenting with ischemic stroke, heart failure, or syncope, only to discover that asymptomatic AF is the underlying etiology.

Healey et al report on a population of hypertensive seniors in whom either a pacemaker or defibrillator had been implanted but who had no prior history of AF (n = 2580). The implanted devices were programmed to report any episode of heart rate 190 beats per minute (bpm) or greater. Subclinical atrial tachyarrhythmia — defined as an asymptomatic occurrence of atrial rate > 190 bpm for more than 6 minutes — was detected in 35% of study subjects over 2.5 years of observation; asymptomatic episodes far outnumbered symptomatic tachyarrhythmia. The risk for ischemic stroke in persons experiencing any atrial tachyarrhythmia was increased by 2.5 fold.

These data may help to explain some of the ischemic stroke cases that have no immediately visible antecedent. On the other hand, the complex terminology that separates AF into persistent, paroxysmal, subclinical, permanent, etc, may not be helpful; the phrase "once a fibber, always a fibber" simplifies the fact that (except for transient AF associated with perioperative stress), any episode of AF, regardless of duration or extinguishability, elevates thrombotic risk. ■

Predicting Adverse Outcomes in Asthmatics: The Severity of Asthma Score

Source: Eisner MD, et al. Severity of asthma score predicts clinical outcomes in patients with moderate to severe persistent asthma. *Chest* 2012;141:58-65.

IN THE UNITED STATES, APPROXIMATELY 5,000 persons die each year from asthma. Several metrics for predicting outcomes in asthmatics are available including the asthma control test, work productivity and impairment index-asthma, FEV_1, and severity of asthma score (SOA). The SOA score is a validated questionnaire that incorporates asthma symptom frequency, medication use history, and hospitalizations for asthma among its 13 items. The Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma study is an observational study of omalizumab or placebo in asthmatics with demonstrated inhalant allergen sensitivity. In the placebo arm (n = 2878), the SOA score was compared with the other metrics mentioned above for its ability to predict five asthma-related outcomes: exacerbations, hospitalizations, unscheduled office visits, emergency room visits, and need for systemic steroid treatment.

Of all the metrics chosen, SOA had the best predictive capacity, and was singular in that it had significant positive-predictive value for all five of the adverse asthma-related outcomes, whereas other tools were positively predictive in only a portion of the five outcomes. One of the attractive aspects of the SOA is that no special tools, lab tests, or measurements of pulmonary function are required to score it. ■

Real-life Use of Sunscreen in Ski Areas

Source: Buller DB, et al. Compliance with sunscreen advice in a survey of adults engaged in outdoor winter recreation at high-elevation ski areas. *J Am Acad Dermatol* 2012;66:63-70.

CURRENT RECOMMENDATIONS FOR SUNscreen include three fundamental steps: 1) application up to 30 minutes before exposure, 2) use of a sun protection factor (SPF) of at least 15 (higher if ultraviolet [UV] radiation is high), and 3) reapplication every 2-3 hours. Skiing is associated with high UV exposure because of the combination of altitude and snow reflection.

Buller et al interviewed adult skiers in the western United States and Canada (n = 4837). Subjects were interviewed face-to-face while riding on chairlifts and gondolas (I don't ever remember getting offered one of those tough, technical scientific jobs!).

Almost 50% of subjects reported using sunscreen with SPF 15 or higher, and most applied it 30 minutes before sun exposure. Reapplication was only performed by 20%. Only 4% of respondents fulfilled all three components of appropriate sunscreen use. Overall, men were substantially less compliant than women.

Messages about the importance of skin protection appear to be reaching the public, including young athletic adults. Further education about the need for reapplication, coupled with insights about circumstances of increased exposure risk (like skiing), might improve compliance in the future. ■

In Future Issues:

Postoperative Complications in Patients with Obstructive Sleep Apnea