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A Cutting Edge Question

ABSTRACT & COMMENTARY

Synopsis: *This study confirms that both nocturnal wrist splints and surgical release are effective options of treatment and suggests that surgical release is more effective in treating carpal tunnel syndrome.*

Source: Gerritsen A. *JAMA*. 2002;228:1245-1251.

THIS RANDOMIZED CONTROLLED STUDY COMPARED SURGERY VS nocturnal wrist splints in 176 patients with idiopathic carpal tunnel syndrome. The primary outcome was self-reported improvement in symptoms as assessed with a general improvement scale at 18 months.

Sixty-eight of the 87 patients assigned to receive open tunnel release and 79 of 87 patients assigned to 6 weeks of nocturnal wrist splints returned for follow-up at 18 months. Ninety percent of the patients assigned to receive surgery reported improvement in the pain scale; 75% of the nocturnal splint group reported improvement (mean difference, 15%; 95% CI, 3-27%; $P = 0.02$). Fifty-three percent of the surgical and 46% of the splint group reported adverse effects. In comparing the 2 therapies, 7 patients would have had to be treated with surgery instead of splints to see 1 clinical improvement (NNT = 7); one additional adverse effect can be expected for every 14 patients who were treated with surgery instead of wrist splints (NNH = 14).

COMMENT BY JEFF WIESE, MD

Carpal tunnel syndrome afflicts between 1-9% of adults. Pain, paresthesias, or weakness results from compression of the median nerve by the overlying fascia. Symptoms are exacerbated by nocturnal wrist flexion during deep sleep and may persist into waking hours. This study confirms that both nocturnal wrist splints and surgical release are effective options of treatment and suggests that surgical release is more effective in treating carpal tunnel syndrome.[1,2]

The results of this study should be interpreted with caution, however. In this study, 326 patients were initially enrolled, but only 176 patients completed the trial. The 111 patients who did not meet inclusion criteria by way of nerve conduction studies may represent

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a cohort with less severe disease who may have been adequately treated with the more conservative treatment option of wrist splinting. The study subjects in this trial may represent a population with more severe disease, and therefore, would be more amenable to surgical intervention.

This study also had considerable dropout; 39 subjects were excluded or refused participation, and another 29 subjects withdrew or did not follow up at 18 months. Because the reason for withdrawal or refusal to participate is unknown, the validity of this study may be tarnished.

The American Academy of Neurology (AAN) recommends that all patients first attempt a trial of wrist splints prior to surgical release.[3] While this trial demonstrates that surgery is more successful than wrist splinting, there was still considerable success with wrist splinting (75%) and less adverse effects. There also does not appear to be an adverse risk for engaging in a trial of wrist splinting prior to surgical release. However, this trial suggests that many of the patients who first try wrist splinting will ultimately require surgical release (41%). ■

References

1. Gerritsen A, et al. *J Neurol*. 2002;249:272-280.
2. Manente G, et al. *Muscle Nerve*. 2001;24:1020-1025.
3. American Academy of Neurology. *Neurology*. 1993;43: 2406-2409.

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $20. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $289
(Student/Resident rate: $145).

Multiple Copies
1-9 additional copies: $215 each; 10 or more copies: $191each.

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Internal Medicine Alert has been approved by the American Academy of Family Physicians as having educational content acceptable for prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of January 1, 2002. This volume has been approved for up to 40 prescribed credit hours. Credit may be claimed for one year from the date of this issue.
The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours.

Statement of Financial Disclosure

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Aspirin: Good for the Heart, Better for the Pain

ABSTRACT & COMMENTARY

Synopsis: *Intake of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), but not of aspirin, is associated with an increased risk of hypertension in women.*

Source: Curhan GC, et al. *Arch Intern Med*. 2002;162: 2204-2208.

THIS REPORT COMES FROM THE NURSE'S HEALTH Study, a prospective study of 116,671 female registered nurses enrolled in 1989. Every other year, this cohort receives questionnaires inquiring about health and lifestyle. In 1995, a subset (n = 91,744) of the entire cohort completed a longer version of the questionnaire, which collected detailed information about the use of aspirin, NSAIDs, and acetaminophen. There were 5 response categories for frequency of use (in days per month) of each of the 3 classes of analgesics: none, 1 to 4, 5 to 14, 15 to 21, and 22 or more. No data on the number of tablets a day or the dose were collected. Multiple other variables were collected and controlled for, including age, weight, smoking, family history, oral contraceptive use, and intake of alcohol sodium, potassium, and magnesium. The questionnaires queried participants about physician-diagnosed hypertension. Women who reported hypertension on any biennial questionnaire up to and including the 1995 questionnaire were excluded from analysis. Thus, women who first reported hypertension on the 1997 questionnaire were included in this analysis. Incidence of hypertension was the number of events (of new hypertension) divided by person-years of follow-up, which was broken down according to frequency of analgesic use. Relative risks (RRs) were cal-

culated as the incidence rate of hypertension in a particular exposure (to analgesics) category divided by the corresponding rate in the comparison category. RRs were adjusted for age and potentially confounding variables.

Of the group, 51.2% used aspirin, 76.7% used NSAIDs, and 72.5% used acetaminophen at least 1 d/mo. Mean age, mean body mass index (BMI), and the proportion of women with a family history of hypertension increased with increasing frequency of analgesic use, but sodium and alcohol intake did not.

After controlling for potential confounders, intake of aspirin was not statistically associated with hypertension (although it was associated with hypertension before adjusting for other potential risk factors, including use of NSAIDs and acetaminophen).

The age-adjusted RR of hypertension was significantly increased, in a dose-dependent manner, for women who consumed NSAIDs or acetaminophen, compared with nonusers. The RR for hypertension in women taking NSAID's or acetaminophen > 22 d/mo was 1.86 (CI, 1.51-2.28) and 2.00 (CI, 1.52-2.62) respectively.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

In case you are thinking that pain causes hypertension (my first thought), Curhan and colleagues point out that all 3 categories of analgesics would likely have been associated with increased blood pressure if that were the case. They also noted an increased risk of hypertension at low levels of analgesic use (1-4 d/mo), which would be an unusual pattern of treatment for chronic pain. They speculate that NSAID use might result in hypertension by causing inhibition of vasodilatory prostaglandins, sodium retention, or increased endothelin 1. They further speculate that acetaminophen use might result in hypertension by causing inhibition of cyclooxygenase, prostaglandin, or nitric oxide. In other words, it's a mystery.

Although several other studies have examined the relationship between analgesic use and blood pressure, this is the first prospective one to look at all 3 classes of over-the-counter analgesics. Aspirin has been exonerated in 2 previous meta-analyses.[1,2] There are very little data about acetaminophen use and hypertension, but NSAIDs have previously been implicated.[1-3]

The use of analgesics in this cohort of relatively young (aged 31-50 in 1989) women is high; more than 70% of the cohort consumed either NSAIDs or acetaminophen at least 1 d/mo. One approach that clinicians can take is to counsel those patients who are not aspirin sensitive to take aspirin, not acetaminophen or NSAIDs, for pain (and, of course, for their hearts). ■

References

1. Johnson AG, et al. *Ann Intern Med*. 1994;121:289-300.
2. Pope JE, et al. *Arch Intern Med*. 1993;153:477-484.
3. Gurwitz JH, et al. *JAMA*. 1994;272:781-786.

'Mad Deer Disease': Another Reason to Become a Vegetarian?

ABSTRACTS & COMMENTARY

Synopsis: *The emergence of chronic wasting disease, a transmissible spongiform encephalopathy in North American cervids, raises concern about potential transmission to humans, as has occurred elsewhere with bovine spongiform encephalopathy and vCJD.*

Sources: Wisconsin deaths may be first instance of 'mad deer' disease transmission to humans. Reuters Medical News. July 31, 2002; Regalado, A. Spreading 'mad deer' plague leaves US scientists baffled. *The New York Times*. May 2002; http://www.maddeer.org/plague.html; http://www.madison.com/captimes/opinion/column/guest/23628.php;McCombie, B. Who is to blame for mad deer? *The Progressive*. August 2002; www.progressive.org/August%202002/mcco0802.html; Mad deer disease spreads across the USA—Hunters are starting to worry. *Outdoor Life*. Oct 1999; http://www.organic-consumers.org/Meat/maddeerusa.cfm;McCombie B. Stop the madness. Malady threatens Wisconsin's elk, deer and, ultimately, people. *Isthmus Newspaper*. Madison, WI, July 2000. http://www.madison.com/captimes/opinion/column/guest/23628.php.

THREE DEER HUNTERS, AGE 30 AND YOUNGER, FROM Utah, Oklahoma, and Maine died of Creutzfeldt-Jakob disease (CJD) during the period of 1997-2000. This raised an alarm since the national occurrence of CJD is approximately 1 per million and generally affects older people. Because of the common variable of consuming deer meat, autopsies were performed to confirm the diagnoses. The results of the autopsies demonstrated that the 3 had died of sporadic CJD and not the more "virulent" form of variant CJD (vCJD). More recently, the Centers for Disease Control and Prevention (CDC) is helping the Wisconsin health department review the cases of 3 hunting partners who died in the 1990s (2 in 1993 and 1 in 1999) of rare brain disorders.

vCJD, also known as "mad cow disease," is responsi-

ble for somewhere between 43 to more than 100 deaths in Europe; numbers vary depending on the source of information that is reviewed. Concern over vCJD is that it has a shorter incubation period and affects people at an earlier age.

Chronic wasting disease (CWD) is a variant of the mad cow disease that has been reported in deer and elk. CJD and CWD are classified as transmissible spongiform encephalopathy (TSE). The "infectious" agent associated with TSE is a small, relatively stable protein known as a prion. Prions are normally folded in a loopy pattern resembling a corkscrew, but when they unfold, they can cause other prions to change shape. This triggers the chain reaction that ultimately results in destruction of tissue, typically in the brain.

CWD was first noticed in a Colorado research facility in 1967 and slowly spread among wild deer and elk in Nebraska and Wyoming. It has also been found in captive elk in Colorado, Kansas, Montana, Nebraska, Oklahoma, Saskatchewan, and South Dakota. In Colorado at least 15% of some wild herds are affected. Because it has also been found in animals imported into Wisconsin, authorities there recommend following the lead of Montana which placed a moratorium on the importation of all game farm animals. Testing of animals in Wisconsin was negative in 1999, but in 2001, 3 animals tested positive for CWD.

The Food and Drug Administration has gone on record saying that mad deer disease is not a threat in the United States. Dr. Ermias Belay of the CDC told a panel investigating this that the cases "suggest a possible relationship with CWD," but investigations found "no strong evidence of a causal link" with the patients' illnesses. The FDA has now suggested, however, that significant efforts be undertaken to remove the CWD from the US deer and elk populations.

COMMENT BY THOMAS G. SCHLEIS, MS, RPh

Tom Thorn, a Wyoming state veterinarian, when discussing CWD stated that "You cannot say with 100 percent certainty that it won't transmit to people, but there is no evidence that it will transmit to people." That essentially sums up the wealth of knowledge we have about mad deer disease—maybe it's a threat, maybe it's not.

The list of TSEs is becoming extensive. We have scrapie in sheep, mad cow, mad deer, mad elk, CWD, CJD, and vCJD.

Having grown up in Wisconsin where the 4 favorite pastimes are eating, drinking, watching television, and hunting, I can only imagine the effect this information has had in that state. Wisconsin has approximately 100 deer and elk farms, and it is big business with elk calves selling for around $1,500 and bull breeding garnering as much as $20,000. Farms sell venison; and the velvet that peels from new elk antlers are considered an aphrodisiac in Asia, selling for $17.00 an ounce. Hunting guides can also package tours that cost from $1,000 to $10,000 depending on the ultimate "prize." This is a billion dollar industry with hunters killing close to half a million deer annually. With no mandatory reporting required for animals suspected of CWD, the disease could go unchecked for years.

What is important here is that this phenomenon be thoroughly investigated. Lab studies have suggested that CWD could theoretically infect humans by converting human prion proteins into their deadly form in a lab dish after exposure to CWD prions. If we have learned anything from mad cow disease, it is that denial can be deadly. With mad cow disease, it was years before British officials were convinced that there was a causal link and appropriate action was taken. It is vital that we do not allow the same mistake to happen here. ■

Dr. Schleis is Director of Pharmacy Services, Infections Limited, Tacoma, Wash.

Do Statins Really Cause Muscle Symptoms?

ABSTRACT & COMMENTARY

Synopsis: *Muscle complaints with normal CPK levels can be seen in patients treated with statins.*

Source: Phillips PS, et al. *Ann Intern Med*. 2002;237: 581-585.

Hydroxy-3-methylglutaryl coenzyme a (HMG-CoA) reductase inhibitors (statins) have proven to be extraordinarily effective and safe when used for the treatment of hypercholesterolemia[1-3] and, outcome studies have clearly demonstrated their effectiveness in the primary and secondary prevention of myocardial infarctions and strokes. However, a small fraction of the millions of people in the United States who are being treated with statin drugs may develop severe myopathy, which, in the worst cases, can lead to severe myoglobinuria, acute renal failure, and even death; in fact, this complication was associated with a number of deaths which led to the recent withdrawal of cerivastatin from

the US market. Toxic myopathy occurs in only approximately 0.1% of statin users and is usually associated with an elevated creatinine phosphokinase (CPK), however less severe forms of myopathy characterized by diffuse muscular pains, fatigue, and weakness associated with, at most, minimal elevation of serum CPK values undoubtedly occur. In these cases the myopathy usually resolves when statin therapy is discontinued.

Phillips and associates investigated complaints of muscle symptoms in 4 patients who were being treated with statins but whose CPK levels were normal and whose symptoms disappeared during placebo use. They were subjected to muscle strength testing and percutaneous muscle biopsies. The end points of the study were 1), whether the patients could accurately identify blinded statin therapy; and 2), the careful evaluation of functional capacity and muscle strength. All 4 patients proved capable of distinguishing blinded statin from placebo therapy based on their symptoms or lack thereof. In addition, the abnormal muscle biopsies that demonstrated evidence of mitochondrial dysfunction when the patients were on statin therapy reversed in the 3 patients who had repeated biopsies obtained when they were not receiving statin therapy.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

Drug manufacturers and the press have successfully educated the millions of patients who use statin drugs with respect to the benefits, safety profile, and especially, with respect to the ability of these drugs to produce muscle symptoms, including severe muscle toxicity. Since major controlled clinical trials have not detected a higher prevalence of muscle symptoms during statin therapy when compared to placebos, most practitioners have characteristically simply reassured patients that their muscular aches and pains were most likely not due to the statin therapy, especially if serum CPK determinations proved to be normal. However, Phillips et al have now clearly and objectively demonstrated that increasing muscular aches and pains often associated with decreased exercise tolerance may, in fact, be due to statin therapy even in patients with normal CPK determinations although, in most cases, the symptoms may not even be consistent with chronic myopathy or be temporally related to statin drug therapy. The clinical, pathologic, histochemical, and biochemical features of the 4 studied patients suggest that an adverse drug reaction did indeed occur; however, it should be clearly recognized that the study results are of limited value because of the small number of patients studied and because the pathologists were not blinded.

Little is known about the mechanism of statin-associated myopathy, although this extremely small study suggests that is due to a defect in mitochondrial chain function. Carefully controlled biochemical, genetic, and pathologic studies in a larger series of patients will be needed to clearly determine the cause of statin-associated myopathy; however, in the vast majority of patients who report muscular symptoms while on statin therapy, chronic or subacute myopathy is not present and therapy should, in most cases, not be discontinued unless the CPK becomes significantly elevated.

In summary, the proven efficacy of statin therapy for primary and secondary prevention of cardiovascular disease far outweighs the unlikely possibility of permanent muscle damage or other more severe complications of severe myopathy. In particular, high-risk cardiovascular patients should not be denied therapy with a drug that has been demonstrated to result in major cardiovascular risk reduction simply because they complained of symptoms that have not been clearly documented to be related to statin therapy.[4] ■

References

1. The long-term intervention with pravastatin in ischemia disease (LIPID) study group. *N Engl J Med*. 1998;339:1349-1357.
2. Scandinavian Simvastatin Survival Study. *Lancet*. 1994;344:1383-1389.
3. Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009.
4. Grundy GM. *Ann Intern Med*. 2002;137:617-618.

Pharmacology Update

Ezetimibe (Zetia—Schering): A New Cholesterol-Lowering Medication

The FDA has approved the first drug in a new class of cholesterol-lowering medications. Ezetimibe works by inhibiting the absorption of cholesterol by the small intestines and is approved for monotherapy or for use in combination with a statin. Ezetimibe will be marketed jointly by Merck and Schering-Plough under the trade name Zetia.

Indications

Ezetimibe is indicated (as monotherapy or in combination with HMG CoA reductase inhibitors) as adjunctive therapy to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol, and

apolipoprotein B in patients with primary hypercholesterolemia. Ezetimibe is indicated in combination with atorvastatin or simvastatin in the treatment of patients with homozygous familial hypercholesterolemia. It is also indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.[1]

Dosage

The recommended dose is 10 mg once daily. It may be taken without regard to meals. Dosage adjustment is not required in patients with mild hepatic dysfunction, renal dysfunction, or in geriatric patients.[1] It may be taken the same time as the HMG CoA reductase inhibitor (statin), as no significant pharmacokinetic interactions have been seen with currently marketed statins.[1]

Ezetimibe is available as 10-mg tablets.

Potential Advantage

Ezetimibe provides a cholesterol-lowering drug with an entirely different mechanism than currently available medications. It and/or its phenolic glucuronide acts on the brush borders of the small intestines by inhibiting the uptake of dietary and biliary cholesterol.[2] Ezetimibe can effectively be combined with a statin such as atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia.[1,4]

Potential Disadvantages

In clinical studies, the incidence of consecutive elevations of liver enzymes (3 x ULN) was higher in combined therapy with a statin than with statin therapy alone (1.3% compared to 0.4%).[1] The long-term safety and effectiveness is not known as controlled clinical trials were only up to 12 weeks in duration. The efficacy and safety of ezetimibe in non-Caucasians is not known, as the clinical evidence in this population is very limited. The safety and efficacy of concomitant use of ezetimibe and fibrates have not been established. Fenofibrate and gemfibrozil have been shown to increase ezetimibe concentration by 1.5- and 1.7-fold, respectively. In addition, the combination may increase the risk of cholelithiasis.[1] Cholestyramine decreases the absorption of ezetimibe by 55%. Ezetimibe should be dosed at least 2 hours before or 4 hours or more after administration of a bile sequestering agent.[1] One renal transplant patient had a 12-fold increase in ezetimibe level while on cyclosporine and other medications.[1]

Comments

Ezetimibe is a new cholesterol-lowering drug with an entirely new mechanism. It acts at the brush border of the small intestine, inhibiting the absorption of dietary and biliary cholesterol. The drug's labeling is mainly based on 2 12-week, double-blind, placebo-controlled studies in 1719 patients with primary hypercholesterolemia and an 8-week study in 769 patients with coronary risk factors currently receiving statin monotherapy but have not at target LDL-C goal. As monotherapy, ezetimibe has been shown in placebo-controlled 12-week studies to produce mean reduction of total cholesterol of approximately 13%, LDL cholesterol by 18%, apolipoprotein B by 16% and triglycerides by 8%.[1,2] Cholesterol reduction is similar to that achieved with a low dose statin (eg, lovastatin 10 mg, pravastatin 10 mg). The effect is seen as early as 2 weeks. In combination therapy with a statin, an additional reduction in LDL-C of 7-19% was achieved.[1] The greater additive effect generally occurred with the lower doses of the statin and decreased as the dose of the statin increases.[1] The drug also lowers triglycerides and raises HDL-cholesterol, but these effects are generally modest to minimal.[1,5,6] Ezetimibe appeared to be well tolerated based on clinical trial data. The incidence of elevated liver enzymes may be higher when ezetimibe is combined with a statin but the combination does not appear to increase the rate of elevated creatine kinase.[1] Long-term safety and efficacy has not been established. The wholesale cost of ezetimibe is $1.93 per day, which is similar to the cost of simvastatin 20 mg or atorvastatin 10 mg.

Clinical Implications

Statins are currently the most effective drugs for the lowering of total cholesterol, LDL-cholesterol, and non-HDL cholesterol. These drugs have demonstrated efficacy in primary and secondary prevention of coronary events and death.[7-11] They are and should remain the first-line drugs. When lipid targets cannot be achieved with dose titration or use of a statin is limited by tolerance, other drugs, such as niacin or bile sequestering agents, are added to the regimen. The approval of ezetimibe provides an agent with a different mechanism of action to use as a complement to the action of a statin. ■

References

1. Zetia Product Information. Schering Corporation. October 2002.
2. Dujovne CA, et al. *Am J Cardiol*. 2002;90(10): 1092-1097.
3. Sudhop T, et al. *Circulation*. 2002;106:1943-1948.
4. Gagne C, et al. *Circulation*. 2002;105:2469-7245.
5. Bays HE, et al. *Clin Ther*. 201;23:1209-1229.

6. Kosoglou T, et al. *Br J Clin Pharmacol*. 2002;54: 309-319.
7. Shephard J, et al. *N Engl J Med*. 1995;333:1301-1307.
8. Downs JR, et al. *JAMA*. 1998;279:1615-1622.
9. Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344:1383-1389.
10. Sacks, et al. *N Engl J Med*. 1996;335:1001-1009.
11. LIPID Study Group. *N Engl J Med*. 1998;339: 1349-1357.

CME Questions

27. Which of the following is true for a 25-year-old woman presenting with carpal tunnel syndrome?

a. Surgical release is the most efficacious option and should therefore be the first line of therapy offered.
b. There is no difference in the efficacy of surgical release and nocturnal wrist splinting. Either option is acceptable.
c. The patient should be offered a trial of nocturnal wrist splinting followed by surgical release should this fail.
d. The patient should receive occupational training and daytime splints; nighttime splints are ineffective and not worth the inconvenience.

28. Which of the following relationships was reported from the Nurses Health Study regarding analgesic use and hypertension?

a. Intake of nonsteroidal anti-inflammatory drugs and acetaminophen, but not of aspirin is associated with an increased risk of hypertension in women.
b. Intake of nonsteroidal anti-inflammatory drugs, but not of acetaminophen or aspirin, is associated with an increased risk of hypertension in women.
c. Intake of acetaminophen, but not of nonsteroidal anti-inflammatory drugs or aspirin, is associated with an increased risk of hypertension in women.
d. Intake of aspirin, but not of nonsteroidal anti-inflammatory drugs or acetaminophen, is associated with an increased risk of hypertension in women.
e. Intake of nonsteroidal anti-inflammatory drugs, acetaminophen, and aspirin is associated with an increased risk of hypertension in women.

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By Louis Kuritzky, MD

Effects of Losartan on Cardiovascular Morbidity and Mortality in Patients with Isolated Systolic Hypertension and LVH

Since the early 1990s it has been recognized that left ventricular hypertrophy (LVH) is an important prognostic indicator for cardiovascular morbidity and mortality. More recently, it has been suggested that angiotensin receptor blockers (ARBs) might exert a particularly favorable effect upon LVH, perhaps even independent of blood pressure (BP) effects. The LIFE (Losartan Intervention for Endpoint Reduction) study was designed to test the hypothesis that losartan (LSN) exerts preventive cardiovascular effects, beyond simply controlling BP. To this end, a randomized, controlled trial (n = 1326) of LSN vs atenolol (ATN) was initiated in persons with isolated systolic hypertension and LVH, with a primary composite end point of cardiovascular death, stroke, and MI.

Despite the fact that BP reduction was equal in both groups (28/9 mm Hg), there was a 25% relative risk reduction in the primary end point (CV death, stroke, MI) in favor of losartan. Additionally, LVH reduction was much more vigorously achieved by LSN than ATN. Stroke reduction was particularly favorably affected by LSN, in which a 40% reduction compared to ATN was seen. Lastly, LSN demonstrated a more favorable tolerability profile than ATN: discontinuations due to drug-related events were half as frequent in recipients of LSN than ATN. ■

Kjeldsen SE, et al. JAMA. 2002; 1491-1498.

Increase in Nocturnal Blood Pressure and Progression to Microalbuminuria in Type 1 Diabetes

It has been noted that among persons with type 1 diabetes (DM-1), hypertension (HTN) often develops concomitantly with occurrence of microalbuminuria (MAU). Closer investigation with ambulatory BP monitoring (ABPM) suggests that nocturnal blood pressure elevations (NBP) are particularly associated with MAU; however, whether the NBP causes the MAU (or they are concomitant) has been uncertain.

Lurbe and associates prospectively studied ABPM in adolescent DM-1 patients (n = 75) who were normoalbuminuric and normotensive at enrollment. Subjects were periodically monitored by ABPM and urinary albumin measurements for more than 5 years. MAU developed in 19% of study subjects, and was preceded by a modest elevation in BP, but it was only the NBP in which change was manifest. Over time, in the group that ultimately developed MAU, the NBP increased by 5 mm Hg compared to baseline; in the normoalbuminuric group, NBP did not change. The subtlety of these findings is reflected by the fact that neither office BP, nor mean daytime BP predicted MAU. Hence, ABPM may detect modest BP patterns, which lead to early prediction of target organ damage. ■

Lurbe E, et al. N Engl J Med. 2002; 347:797-805.

HRT, Lipid, and Glucose Metabolism in Diabetic and Nondiabetic Postmenopausal Women

Like cardiovascular diseases, type 2 diabetes (DM-2) increases in postmenopausal women. Prospective randomized interventional trials have not shown a benefit for hormone replacement therapy (HRT) in improving cardiovascular outcomes. The effect of HRT upon lipids and glucose among diabetic populations has been little studied. Crespo and colleagues evaluated subjects (n = 2786) in the Third National Health and Nutrition Examination Survey (NHANES III) seeking the relationship between HRT, diabetes, and lipids.

In diabetic women, total cholesterol and non-HDL levels were significantly lower in women who used HRT than never users, but there was no difference in HDL levels. In contrast, in nondiabetic women HDL levels were higher in HRT users than nonusers. Fasting glucose levels (FBS) in diabetic women were significantly lower in HRT recipients than never users (112 mg/dL vs > 150 mg/dL). Crespo et al conclude that menopausal HRT is associated with improved FBS, total cholesterol, and non-HDL in diabetics. The fact that these findings are observational in nature suggests cautious interpretation until their clinical relevance is ascertained through interventional trials. It may be that other, undetected factors in women who choose to use HRT are influencing lipid and glucose metabolism. ■

Crespo CJ, et al. Diabetes Care. 2002;25:1675-1680.

In Future Issues: Suspected Pulmonary Embolism in Pregnancy