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INSIDE

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LDL Lowering—Should Ezetimibe Ever Be Used?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationship to this field of study.

Synopsis: Lifestyle changes such as improving diet and exercise are always the first important approach for the treatment of hyperlipidemia however, if the target LDL-C level is not achieved using statins and niacin, fibrates, and/or resins, at this time, ezetimibe should definitely be utilized to achieve these target goals if there are no specific contraindications to the use of the drug in each individual patient.

Source: Brown BG, et al. *Curr Opin Lipidol.* 2006;17:631-636.

Lower is better HAD BEEN THE BATTLE CRY WITH RESPECT TO LDL-cholesterol (LDL-C) for close to 20 years since most controlled clinical trials of statins have demonstrated the validity of that conclusion because of both the clinical and imaging cardiovascular benefits which had been widely reported to occur when LDL-C is adequately lowered.[1] In fact, it would even appear that the magnitude of the event reduction is a function of the extent of LDL-C lowering.[8] However, since administration of even the highest approved dosage of statin drugs used for LDL-C lowering not infrequently offered less than optimal lowering of the LDL-C and/or were, on occasion, associated with an increased incidence of side effects,[2] other drugs which further reduced LDL-C levels either alone or when added to statin therapy were sought for and eventually developed. Ezetimibe is such a drug which acts by inhibiting cholesterol absorption from the gastrointestinal tract resulting in lower cholesterol and LDL-C levels. It has frequently been combined with statin drugs in clinical practice and has been demonstrated to provide further incremental reduction of LDL-C levels of 12-19%[3-4] beyond the levels of LDL-C reduction obtained with statin drugs alone

Kastelein and his colleagues for the ENHANCE (ie, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial) investigators[5] sought to determine over a two-year period of time whether daily therapy with 80 mg of simvastatin plus

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either placebo or 10 mg of ezetimibe could reduce the progression of atherosclerosis in patients with familial hypercholesterolemia as assessed by measurement of arterial intima-media thickness. The rationale for studying patients with familial hypercholesterolemia was that these patients have a greatly increased risk of premature coronary artery disease[6] and an increased rate of progression of intima-media thickness starting in childhood.[7] The study demonstrated that, in patients with familial hypercholesterolemia, combined-therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima-media thickness, as compared with simvastatin alone, despite decreases in levels of LDL-C and C- reactive protein.

COMMENTARY

Intima-media thickness has been well validated as a surrogate marker for atherosclerotic vascular disease in published results from large epidemiologic studies which have demonstrated strong associations between intima-media thickness and stroke, angina pectoris, and myocardial infarction.[6,7] Considering the results of the ENHANCE study, should we conclude that the addition of ezetimibe to a high-dose statin is very effective in lowering LDL-C but had no added value in the therapy of atherosclerosis and presumably therefore has no clinical benefits? Before answering this important question, it is important to recognize that over the past two decades most patients with familial hypercholesterolemia will have received statins, resins, ezetimibe or various combinations of these agents with increasing intensity starting at early ages. It should also be recognized that any long-term drug therapy which had been given before entering a trial may have favorably altered the atherosclerotic plaque resulting in plaque stability and clinical quiescence[9] and therefore, only minimal changes in plaque thickness might be expected with subsequent ezetimibe therapy although it should be noted that the 19% of patients who were not receiving statins at the time of ENHANCE enrollment did not have a better response with the combined regimen of simvastatin plus ezetimibe compared to those receiving simvastatin alone. In further support of the influence of previous statin therapy on the progression of intima—media thickness in the carotid artery, it had previously been reported that progression of media thickness in the carotid artery decreased to only 0.005 mm per year during long-term daily therapy with 80 mg of atorvastatin, a finding that contrasts with the substantial reductions in intima-media thickness which had occurred during the first two years of the trial.[10] Finally, the RADIANCE 1 study[11] in a similar group of patients revealed a similar pattern of change in the intima-media thickness in patients receiving a mean daily dose of 57 mg of atorvastatin raising the possibility that there may be limits to the extent to which the lowering of LDL-C levels can result in a further decrease or in the progression of intima-media thickness in the group of patients who had received previous statin therapy and who have only a modest baseline intima-media thickness to begin with.

Ongoing clinical trials such as the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) will hopefully help to define the role of ezetimibe in the treatment of hypercholesterolemia and should also provide insight into the biology of LDL-C lowering and the use of carotid intima-media thickness as a surrogate indicator of coronary events. However, the results of the IMPROVE-IT trial will not be available until at least 2011 and therefore, in the interim, clinicians should continue to evaluate and treat their patients by first determining the target LDL-C that they want to achieve in a particular patient based upon the clinical picture and risk factors presented by that patient. The National Cholesterol Education Program Adult Treatment Panel-III targeted the optimal LDL-C levels for patients with coronary heart disease (CHD) or CHD risk equivalents (ie, diabetes, peripheral or cerebral vascular disease and/or predicted 10 year CHD risk of greater than 20%) at less than 100 mg/dL (12) and the National Institutes of Health's National Cholesterol Education Program recommended that the-LDL-C level should be reduced to below 70 mg/dL in patients who have suffered a myocardial infarction or who were

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SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

ASSOCIATE PUBLISHER: Lee Landenberger.

MARKETING PRODUCT MANAGER: Shawn DeMario.

MANAGING EDITOR: Iris Williamson Young

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considered to be at high risk for the development of symptomatic CHD. It should be noted that these current guidelines may be replaced by the end of this calendar year by revised ACC/AHA lipid-management guidelines that reflect the results of the ENHANCE trial.

How should the prudent physician use ezetimibe at the present time in his hypercholesterolemic patients? Of course, life style changes such as improving diet and exercise are always the most important first approach for the treatment of hyperlipidemia however, if the target LDL-C level is not achieved using statins and niacin, fibrates, and/or resins, ezetimibe which is relatively safe and extremely effective at lowering LDL-C levels should still definitely be utilized to achieve the target LDL-C goal if there are no specific contraindications to the use of the drug in any individual patient. ■

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So You Took Hormones, Now What?

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky;Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips reports no financial relationship to this field of study.

Synopsis: *For those women who were randomized to estrogen plus progesterone in the Women's Health Initiative Trial, the increased risk of breast cancer has persisted since stopping the replacement therapy, but the increased risk of cardiovascular events has returned to that of the placebo group.*

Source: Gerardo Heiss G, et al. *JAMA.* 2008;299(9):1036-1045.

WHAT HAS HAPPENED TO THE WOMEN IN THE Women's Health Initiative (WHI) study who were randomized to hormone replacement therapy (HRT) since the trial was prematurely terminated? This paper reports the results of continued observation of 15,730 of the original 16,608 women in the WHI trial after HRT was stopped. In brief, treatment in the WHI study consisted of conjugated equine estrogens plus medroxyprogesterone acetate (Prempro), or matching placebo. Standardized information was collected on symptoms, adverse events, adherence to study pills, and potential trial clinical outcomes twice yearly during the intervention phase, which ended July 7, 2002. After the abrupt termination of the treatment part of the study, the investigators continued to follow the women enrolled until March 31, 2005. Follow-up included continued collection of the measures included in the treatment phase, as well as annual mammography. The women in the placebo and HRT groups were not different in baseline characteristics. They had a mean age of 63 years.

After about 3 years of follow-up, the risk of cardiovascular events in the two groups was no longer different, nor were the risks of deep vein thrombosis or pulmonary embolism. However, the "all cancer" risk was higher for the HRT group, driven primarily by an increased risk of invasive breast cancer in the HRT group. The lower risk of colorectal cancer that had been observed during the treatment phase disappeared during the observation period, as did the slightly reduced risk of fractures. There was a statistically insignificant increase in all-cause mortality in the HRT group during the period of follow-up.

■ COMMENTARY

We all remember the furor that resulted when the WHI trial of HRT was stopped in the summer of 2002 after only 5.6 years. The study was terminated because of an increased risk of invasive breast cancer and the failure to demonstrate an overall health benefit, in addition to increased risks of cardiovascular disease (CVD), coronary heart disease (CHD), stroke, and venous thromboembolism in those who were taking HRT.[1] Since that report, guidelines for menopausal hormone therapy have changed[2,3] and use of hormone replacement therapy has declined markedly.

This report gives a glimpse into the future of women who have used hormone replacement therapy, and suggests strategies to minimize ongoing risk. Women can be reassured that risk of cardiovascular disease and death (the leading cause of death for women and men in the US) quickly returns to baseline after cessation of hormone use. On the other hand, the increased risk of malignancy persists, at least for 3 years. Annual mammography and avoidance of other risks for malignancy (smoking, obesity) are especially important for those who have taken or who continue to take hormone replacement. ■

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Ten-Year Update on AAAs

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Dr. Crawford is Professor of Medicine, Chief of Cardiology, University of California, San Francisco.He is editor of Clinical Cardiology Alert*, and is on the speaker's bureau for Pfizer.*

This abstract first appeared in the May 2008 issue of Clinical Cardiology Alert.

Source: Freiberg S, et al. *Circulation*. 2008;117:1010-1017.

ONE-TIME SCREENING FOR ABDOMINAL AORTIC Aneurysms (AAA) is recommended in older men, but there is little long-term data on the value of such screening, especially in women. Thus, Freiberg and colleagues from the Cardiovascular Health Study (CHS) evaluated 4734 men and women over age 65 at enrollment in 1992-1993 who had B-mode ultrasound of the abdominal aorta. Aortic diameter was measured above and below the renal arteries in a standard fashion. Two criteria were used to diagnose AAA: an infrarenal aortic diameter > 3.0 or an infrarenal to suprarenal diameter ratio < 1.2. The subjects were contacted twice a year to obtain medical information. The primary outcome variables were: surgical repair, total mortality, and incident cardiovascular events. One or both criteria for AAA were met by 416 subjects; 13% of men and 6% of women. By 2002, there had been 56 surgical repairs and ten AAA-related deaths (six with surgery). The best predictor of subsequent surgical repair was an infrarenal diameter of > 2.5cm (sensitivity and specificity of 90%). Among those that died, all of their infrarenal aortic diameters were > 6.5 cm and three were > 9 cm. An AAA at baseline was associated with a higher mortality (RR 1.44, 95% C1 1.25-1.66) and more cardiovascular events (RR 1.52, 1.25-1.85). AAA also predicted the presence of chronic kidney disease. Freiberg et al concluded that a one-time screening of men and women over age 65 years for AAA can identify those at risk for AAA complications, cardiovascular events, and death.

COMMENTARY

This study is consistent with previous studies that demonstrated the value of one-time screening for AAA in older men, and affirms the lower prevalence of AAA in women. However, the incidence in women was not inconsequential at 6%. It is not surprising that infrarenal aortic size predicted AAA surgery, complications, and death, but other cardiovascular events were also predicted. It has long been recognized that there was an overlap in aortic disease patients and cardiac disease patients, but it has not been clear whether this was the coincidental association of AAA with the more common atherosclerotic vascular disease spectrum. The confusion arises because we have other diseases of the aorta which can lead to aneurysm formation which have little to do with atherosclerosis (eg, Martens). This study seems to support the same disease spectrum hypothesis. Consequently, AAA screening may identify patients with atherosclerotic vascular disease who need appropriate therapy. An infrarenal diameter > 2 cm would suggest atherosclerosis in this study in men and women. Thus, abdominal ultrasound now joins high-sensitivity CRP, LDL cholesterol, and coronary CT screening as methods for identifying subclinical atherosclerosis. Abdominal ultrasound also identifies AAA which is eminently treatable now, often with percutaneous devices. ■

Viral Influenza Complications

ABSTRACT & COMMENTARY

By Joseph F. John, MD, FACP, FIDSA, FSHEA

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston

Dr. John is a consultant for Cubist, Genzyme, and bioMerieux, and is on the speaker's bureau for Cubist, GSK, Merck, Bayer, and Wyeth.

This abstract first appeared in the May 2008 issue of Infectious Disease Alert.

Source: Rothberg MB, et al. Complications of viral influenza. *Am J Med*. 2008;121:258-264.

CLINICIANS ARE BECOMING MORE ATTUNED TO the many complications of influenza, particularly with the high morbidity and mortality seen with

H5N1 strains spreading around the world. The infectious disease group from Baystate Medical Center in Springfield, MA, has done a good job compiling a modern article on complications of influenza. They organized their summary into several sections.

Risk stratification. The emphasis here is on older age, immunosuppression either endogenously with HIV infection or through organ transplantation. Allograft rejection may be associated with influenza infection

Pulmonary complications. These complications fall into four categories:

• *Primary influenza virus pneumonia.* Up to 18% of patients admitted to the hospital with pneumonia may fall into this group. With H5N1 infection, after an incubation of 3-8 days, symptoms may become extremely severe.

• *Secondary bacterial pneumonia.* Most readers know about the dreaded superinfections with staphylococci and the pneumococcus. Toxic shock may be a byproduct of infection with *S. aureus* associated with influenza. With the national epidemic of community MRSA, that can cause necrotizing pneumonitis itself, clinicians have to be especially wary of progression of disease due to CoMRSA.

• *Infection with unusual pathogens.* The pathogens that we usually do not think about but which can superinfect the flu victim are group B streptococci, *Legionella pneumophila,* and even Aspergillus sp.

• *Exacerbations of COPD.* The mechanism of this complication is poorly understood but treating the underlying influenza infection may forestall this process.

Miscellaneous complications. The most notable of other complications include psychiatric manifestations which have not been well studied, central nervous system involvement that should be documented with CSF analysis, CNS involvement caused by Reye's Syndrome, a non-inflammatory brain process associated with liver failure, and myositis severe enough to produce rhabdomyolysis, probably more common with influenza B.

Vaccine and antiviral medications. Rothberg and colleagues stress here the use of vaccine as the "cornerstone" of prevention of influenza illness but there is not adequacy of data to say that complications are reduced. For that reason, Rothberg et al stress that during an influenza outbreak, viral entry blockers like amantadine and rimantadine along with two neuraminidase inhibitors, oseltamivir and zanamivir, are options for reducing complications. There are many issues of resistance with both classes of antivirals, and we know very little because of the lack of clinical trials, about the true efficacy of these medications in avian influenza.

COMMENTARY

This year has been a tricky one for influenza. The "match" for vaccine versus infection types was not good, so when the final analysis of influenza cases is complete this summer, we are likely to see this has been a difficult year with influenza. As of April 5th, CDC published data have shown that of 34,380 isolates from the United States, only 6.1% were H1 types, 16.3% H3 types, and 51.6% unsubtyped A types. Almost 26% were influenza B viruses. The CDE weekly web site has further information: http://www.cdc.gov/flu/weekly.

New vaccine formulations for the 2008-2009 season will include the Brisbane viruses and B/Florida. The formulation is changed for all three components from the 2007-2008 formulation. Depending on the actual make-up of the unsubtyped viruses, we may see again that the vaccine may not be a good match. According to the CDC web site information, the A/Brisbane H1N1 component represents a recent genetic variant evolved from the A/Solomon Islands/03/2006 virus. The H3N2 A/Brisbane which constituted 71% of 161 H3N2 virus typed by the CDC is a recent antigenic variant from A/Wisconsin/67/2005-like viruses.

Regarding the complications of influenza discussed by Rothberg et al in this article, they suggest that the more novel the infecting virus, for example, H5N1, the more likely may be complications. The pathogenesis of H5N1 may be somewhat unusual. Spread of the H5N1 virus beyond the lung has been suggested, but severe symptoms may relate more to cytokine disregulation (*Emerg Infect Dis*. 2005;11:1036-1041). Thus, the amount of systemic symptoms and signs present may vary with the novelty of the virus. The high mortality rate being seen with circulating H5N1 isolates continues to be of great concern.

Clinicians need to be every wary about the evolution of influenza viruses. Pandemic influenza programs currently envelop our health care institutions; however, there is no way to know when or if we will see pandemic influenza soon. The more subtle changes in both influenza A and B viruses and the sporadic impact of H5N1 strains remain enough of a challenge for health care providers from this season to the next. ■

Pharmacology Update

Certolizumab Pegol Injection (Cimzia®)

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

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

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

ANOTHER MONOCLONAL ANTIBODY TO TNF-α HAS been approved for the treatment of Crohn's Disease. Certolizumab is a pegylated humanized Fab' fragment of an anti-TNF monoclonal antibody. It joins other anti-TNF-α drugs such as infliximab and adalimumab for this indication. Certolizumab pegol is marketed by UCB, Inc as Cimzia.

Indications

Certolizumab is indicated for the treatment of moderately-to-severely active Crohn's disease in patients who have inadequate response to conventional therapy.[1]

Dosage

The initial dose is 400 mg (given as 2 separate 200 mg doses) subcutaneously to separate sites on the abdomen or thigh. The dose is repeated at 2 and 4 weeks after the initial dose. The maintenance dose is 400 mg every 4 weeks. The patients should be tested for latent tuberculosis infection prior to initiating therapy.[1]

Certolizumab is supplied as two 200 mg vials containing powder for reconstitution, diluent, syringe and needle.

Potential Advantages

Certolizumab lacks the Fc portion of the monoclonal antibody, potentially resulting in fewer adverse events. The Fc region binds to various cell components including complement and mediates different immunologic effects such as degranulation of mast cells, apoptosis, and opsonization.

Potential Disadvantages

Certolizumab showed modest improvement in clin cal response over placebo,[2] however it was not statistically better than placebo in terms of remission rate at 6 and 26 weeks.

Comments

The efficacy of certolizumab in adults with moderate-to-severe Crohn's disease was shown in a 26-

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

week, randomized, double-blind, placebo-controlled trial (PRECISE 1) (n = 660). These patients had a baseline Crohn's Diseases Activity Index (CDAI) between 220 and 450. Clinical response was defined as a decrease of CDAI of 100 or more and remission defined as a decrease of 150 or more. At 26 weeks, the response and remission rates were 37% and 29% for certolizumab and 27% and 18% for placebo respectively ($p < 0.05$).[1,2] When both weeks 6 and 26 were considered together, certolizumab was superior to placebo in terms of clinical response (23% vs 16%, $p < 0.05$). However, clinical remission was not statistically different (14% vs 10%). In a second study, patients with response at 6 weeks were randomized to certolizumab (400 mg every 4 weeks) or placebo through 26 weeks (PRECISE 2).[3] Remission was achieved in 48% of certolizumab patients and 29% of placebo patients ($p < 0.05$). As with other anti-TNF agents, certolizumab is less effective in TNF-alpha treatment experienced patients than treatment naïve patients. Most common adverse events are upper respiratory tract infections, urinary tract infection, and arthralgia. As with other anti-TNF drugs, there are risks for serious infections (eg, tuberculosis), malignancies (eg, lymphoma), hypersensitivity reactions, neurologic reactions (demyelinating disease), and hematologic reactions.[1] Development of antibodies to certolizumab and ANA antibodies has been reported. Certolizumab costs $1316 per dose.

Clinical Implications

Anti-TNF agents are indicated for the patient with Crohn's disease who has failed conventional therapy (eg, corticosteroids, immunosuppressives). Certolizumab introduces another anti-TNF agent. Current anti-TNF therapy includes infliximab (chimeric monoclonal antibody), and adalimumab (humanized monoclonal antibody). Infliximab requires intravenous infusion while adalimumab and certolizumab are given subcutaneously. Adalimumab is self-administered and certolizumab should be injected by a healthcare provider. Chimeric monoclonal antibodies may be more immunogenic compared to humanized monoclonal antibodies. Adalimumab has been used successful in some patients who have lost responsiveness or developed intolerance to infliximab.[4] There are no published comparative trials among these three agents at this time. A systematic review of pooled data in placebo-controlled studies reported that these agents showed higher clinical responses than placebo, {RR 2.19 (95% CI; 1.27-3.78)} for infliximab, {RR 2.69 (95% CI; 1.88-3.86)} for adalimumab, and {RR 1.74(95% CI; 1.41-2.13)} for certolizumab.[5] For clinical remission the numbers were {RR 2.50 (95% CI; 1.64-3.80)}, {RR 2.50 (95% CI; 1.37-4.51)}, and {RR 1.68 (95% CI; 1.30-2.16)} respectively. The role of certolizumab in Crohn's disease remains to be determined. ■

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CME Questions

22. Ezetimibe therapy:

a. is never indicated for the treatment of hyperlipidemia.
b. is always indicated for the treatment of LDL-C levels over 130 mg/dL
c. if there are no contraindications, should definitely be utilized if the target-LDL-C level is not achieved by using a statin and/or niacin, fibrates and/or resins.
d. should never be combined with a statin drug.

23. Which of the following is true regarding risks of hormone replacement therapy compared with placebo 3 years after stopping the treatment for women in the Women's Health Initiative?

a. both the increased risk of breast cancer and the increased risk of cardiovascular events persist.
b. neither the increased risk of breast cancer nor the increased risk of cardiovascular events persists.
c. the increased risk of breast cancer persists, but the increased risk of cardiovascular events does not.
d. the increased risk of cardiovascular events persists, but the increased risk of breast cancer does not.

Answers: 22(c); 23(c)

Clinical Briefs

By Louis Kuritzky, MD, *Clinical Assistant Professor, University of Florida, Gainesville*
Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

CAC: A kinder, Gentler Way to Predict Cardiovascular Risk

In 2007, the ACCF/AHA published a consensus statement in the Journal of the American College of Cardiology endorsing a role for coronary artery calcium scoring (CAC) in cardiovascular risk stratification. Because the CAC process is relatively inexpensive, brief, highly reproducibly, non-invasive and supported by multiple large data sets, it holds great appeal.

Detrano, et al studied an ethnically diverse population (n=6,722) comprised of white (38.6%), black (27.6%), Hispanic (21.9%) and Chinese (11.9%) adults over the age of 45. Subjects, who had no known cardiovascular disease at study enrollment, underwent CAC at baseline and were followed for a median of 3.8 years.

During the followup period, 162 major coronary events occurred. Compared to persons without increased CAC scores, the relative risk for coronary events was more than 7-fold higher in persons with elevated CAC scores. There was no discernible difference in the association of CAC score with coronary events between the different ethnic groups. The authors note that the predictive capacity of CAC goes beyond that of traditional risk factors. CAC is not yet universally available, but merits consideration by clinicians. Experts suggest that the greatest utility of CAC is in individuals calculated to be at intermediate coronary risk by traditional scoring, such as Framingham. ■

Detrano R, et al. N Engl J Med. 2008;358:1336-1345.

Was Mae West Right? CV Risk Reduction: Too Much of A Good Thing is Wonderful

The concept that global cardiovascular risk reduction (ie, concomitant lipid, BP, glucose, diet, and exercise interventions) is the most sensible path for success in persons identified as vasculopaths has few detractors. On the other hand, how much of a good thing gets to be too much of a good thing? Despite the counsel of Mae West, increasing intensity of pharmacotherapy is typically associated with increased cost, risk, and complexity, and should be documented to provide meaningful incremental benefit because of the associated increased burdens.

The SANDS trial (Stop Atherosclerosis in Native Diabetics Study) enrolled American Indian type 2 diabetics (n=499) and randomized them to aggressive LDL control (<70 mg/dL) and BP control (<115 mmHG SBP) vs standard therapy (LDL<100, SBP <130). The primary endpoint was progression of carotid artery intimal medial thickness. Clinical events were a secondary endpoint. Carotid IMT was measured at baseline, 18, and 36 months.

There was a statistically significant difference in carotid IMT favoring the intensive intervention group. Left ventricular mass also decreased more with aggressive intervention. Although there was a trend towards fewer CVD events, this difference did not achieve statistical significance, perhaps attributed to the unusually low number of events in the trial as a whole. These data are supportive of aggressive risk factor reduction in diabetics. ■

Howard BV, et al. JAMA. 2008;299(14):1678-1689.

Midlife Contraception

The mean age of attainment of menopause in American women—51 years—has not meaningfully changed over more than a century. During late reproductive life, pregnancy has more adverse consequences than in younger women. The therapeutic abortion rate of post-40 women is higher than any other age group except adolescents. Hence, midlife contraceptive decisions might be weighed differently than at other periods of reproductive life.

Kaunitz reviews multiple factors that impact contraceptive decisions after age 40. DVT risk after age 39 is more than 4-fold greater than in adolescent women, exaggerated further in obese women, in whom progestin-only oral contraceptives might logically be preferred. Older women who smoke should not be prescribed oral contraceptives, and Kaunitz recommends similar restrictions for midlife women with hypertension or diabetes.

Data on risk for breast cancer in association with oral contraceptives is largely reassuring, although data sets usually contain few women over age 45 to study. Oral contraceptives improve bone mineral density, and are associated with reduced risk for ovarian, endometrial, and colon cancer.

No method of discontinuation of contraception has proven ideal in all women. Kaunitz suggests continuing oral contraceptives, if well tolerated, into the early-mid 50s, after which pregnancy risk upon discontinuation is very low. Women who continue to menstruate after that point may use barrier methods. The ideal candidate for midlife oral contraceptives is the lean, slender, nonsmoker. ■

Kaunitz AM. N Engl J Med. 2008;358:12:1262-1270.

In Future Issues:

Omega-3 Free Fatty Acids for the Maintenance of Remission in Crohn's Disease