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INSIDE

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Update on the Controversies of Statin Therapy

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

Synopsis: *After careful evaluation of all the published studies regarding the possible adverse effects of statin therapy, Jukema et al have concluded that there is no proven increased risk of cognitive decline or cancer development. However, there is a possible small increased risk for the development of type 2 diabetes mellitus.*

Source: Jukema JW, et al. The controversies of statin therapy: Weighing the evidence. *J Am Coll Cardiol* 2012;60:875-881.

As is well known, cardiovascular disease is the leading cause of death in industrialized nations.[1] The prevention and avoidance of the progression of cardiovascular disease is critically dependent on lipid-lowering therapy, which has been most often and reliably achieved with 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statin drugs. Statins are now the most widely prescribed class of drugs worldwide, and their widespread use is a major reason for the 25-45% reduction of cardiovascular events in the modern era. They are extremely well tolerated with only minimal adverse side effects, such as transient myopathies and/or elevations of liver enzymes, and on rare occasions, serious rhabdomyolysis may occur with their use.

Earlier this year, the FDA expanded the warning section of all statin drug labels to include the serious risk of liver damage. Although the occurrence of serious liver damage with statin therapy is rare and unpredictable, periodic liver-monitoring tests do not appear to be effective for detecting or preventing liver injury and therefore should not be performed on a frequent basis. However, an increased number of observations have surfaced suggesting that statin use may increase cogni-

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tive decline[2] manifested by memory loss, forgetfulness, and confusion. These events have rarely been reported, have occurred with the use of all statin products and in all age groups, and have occurred in individuals whether they had been taking the medication for only a day or two or for many years. The reported symptoms were generally not serious and were usually reversible within a few weeks of the patient stopping the statin drug.

■ COMMENTARY

Since the introduction of statins in 1987, the association between statin drug use and possible adverse cognitive effects has been carefully studied.[3] Cognitive symptoms reported have included short- and long-term memory loss, behavioral changes, impaired concentration and attention, paranoia, and anxiety. Some scientists have suggested that since cholesterol synthesis is essential for neurons to function normally, the metabolic effects of inhibition of cholesterol synthetic pathways may, in some individuals, result in adverse neurocognitive effects. Jukema and his colleagues[4] identified nine observational studies related to statin use and cognitive function.[5-13] Four studies observed beneficial effects of statins on cognitive performance,[5-8] three studies found no cognitive side effects,[9-11] and two studies found an increased risk of cognitive impairment associated with statin use.[12,13] Of course, it must be clearly recognized that the possible adverse effects of statin drugs noted in these observational studies may be compounded by the fact that the patient population receiving statin drug therapy is usually already at risk for cerebral vascular disease because they are usually older than those not receiving statin therapy and frequently are afflicted with multiple cardiac risk factors. Therefore, by definition, these subjects are more prone to developing cognitive impairment whether they are taking a statin drug or not.[14] Furthermore, statistical correction for imbalances between treatment groups in observational studies has proven to be unreliable.[15]

After careful evaluation of two large, randomized, controlled clinical trials[16,17] on the effects of statin drugs on cognitive function, Jukema et al[4] concluded that there was no solid evidence that statins had a detrimental (or beneficial) effect on cognitive function. Furthermore, after evaluating systematic reviews and large meta-analyses they found that there was no increased risk of incident cancer associated with statin therapy. However, they did note that a recent meta-analysis revealed that those subjects receiving intensive-dose statin therapy compared with those receiving only moderate-dose statins were found to have a higher incidence of new-onset diabetes. They conclude that more research is needed to find the possible underlying mechanism of the observed small statin-related diabetes risk. They also state that the proven large benefit of statin therapy in the primary and secondary prevention of cardiovascular events — especially in diabetic patients — far outweighs the small absolute risk for the development of new-onset diabetes.

In conclusion, after careful evaluation of all of the published studies regarding the possible adverse effects of statin therapy, Jukema et al[4] have concluded that there is no proven increased risk of cognitive decline or cancer development. However, a small increased risk for development of type 2 diabetes mellitus does exist. Because of the overwhelming benefit of statins in the reduction of cardiovascular events, they concluded that the small absolute risk for developing type 2 diabetes is far outweighed by the cardiovascular benefits in patients for whom statin therapy is recommended. ■

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Stroke Risk with Warfarin Interruption

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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Dr. Crawford reports no financial relationships relevant to this field of study. This article originally appeared in the October 2012 issue of Clinical Cardiology Alert.

Synopsis: *The authors concluded that interruption of warfarin therapy in non-valvular atrial fibrillation patients increased the short-term risk of death or thromboembolism, especially during the first 90 days of treatment interruption.*

Sources: Raunso J, et al. Increased short-term risk of thromboembolism or death after interruption of warfarin treatment in patients with atrial fibrillation. *Eur Heart J* 2012;33:1886-1892. Hohnloser S, et al. The hazards of interrupting anticoagulation therapy in atrial fibrillation. *Eur Heart J* 2012;33:1864-1866.

The risk of interrupting prophylactic warfarin for stroke prevention in atrial fibrillation (AF) patients is unclear. Thus, these investigators from Denmark evaluated their national health registry and found 102,591 patients > age 30 with a first-time hospitalization for AF between 1997 and 2008. Valvular AF patients were excluded. Follow-up was started 7 days after hospitalization to ensure achievement of steady-state warfarin dosing. Warfarin therapy was subsequently determined by their national pharmacy database and warfarin usage was estimated based on the supply of medications dispensed. The primary outcome was the combined endpoint of all-cause mortality or hospitalization for thromboembolism. The mean follow-up was 3.5 years. During warfarin therapy, the primary endpoint occurred in 6.9/100 patient-years. At least one treatment interruption occurred in 72% of the patients and these patients had lower CHADS2 scores compared to the no interruption group (1.34 vs 1.56, $P < 0.001$). The median duration of interrupted therapy was 36 days. Among the 16,738 primary events, 49% occurred during the treatment interruption, for a rate of 14.2/100 patient-years. More events occurred during the first 90 days of interruption (31.6/100 patient-years) and leveled off after 180 days. The hazard ratio for treatment interruption was 2.9 (95% confidence interval [CI] 2.8-3.0). Also, the hazard ratio was similar if death was excluded as an endpoint. The authors concluded that interruption of warfarin therapy in non-valvular AF patients increased the short-term risk of death or thromboembolism, especially during the first 90 days of treatment interruption.

■ COMMENTARY

Because of their national health systems, many European countries have very large patient databases that dwarf those at some of our single hospital systems or even multicenter trial databases. Although limited by their retrospective observational nature and the unique structure of national databases, their sheer size makes these analyses important. This study from Denmark has two interesting findings. First, the incidence of warfarin therapy interruption in AF patients is high, about three-quarters of patients, and the median length is relatively long, 36 days. Randomized AF therapy trials have noted interruptions at a frequency of 15-30%. Clearly, real-world experience is very different from trials. Second, the risk of thromboembolism or death rises three-fold in the first 90 days of interrupted therapy, then tapers off. Thus, real world patients on warfarin stroke prophylaxis for AF are often at considerable risk because of therapy interruptions.

Interestingly, there were no subgroup differences in the incidence of the primary event whether stratified by age, sex, duration of therapy, or CHADS2 score. Also, excluding death as an endpoint did not appreciably alter the results, suggesting that the important events were thromboembolism. This raises the question of the etiology of the increase in events. One possibility is that warfarin is preventing strokes and after its withdrawal the stroke rate returns to its natural state (the so-called catch-up phenomenon). Another is that there is a warfarin withdrawal phenomenon that actually increases the rate of thromboembolism over what it would naturally be. Although there are some experimental data showing that coagulation factors transiently rise above normal levels after warfarin withdrawal, there are no clinical mechanistic data to support this theory. Finally, it is possible that whatever occasioned the interruption in therapy was the cause of the

event, such as surgery (confounder). Unfortunately, this study is not able to sort out these potential mechanisms.

Other studies have shown that warfarin can be interrupted for clinical reasons such as surgery or due to patient decisions unrelated to their health conditions. This study does not specify the reasons and we have no clinical data such as INR values. Also, we do not know if the interruptions were transient or the patients stopped therapy. Although the median duration of interruption was 36 days, the 75th percentile was 207 days. Specific guidelines exist for medical issues such as high INR values, episodes of major bleeding, and surgery, which should minimize the risks of thromboembolism, so one could conclude that the majority of the interruptions that lead to events were in the patient decision category. If so, it behooves us to emphasize the importance of continuous therapy to our patients. Perhaps the use of the newer oral anticoagulants, which do not require INR-based management, will improve patient compliance. ■

Biomarkers and the Diagnosis of Alzheimer's Disease

ABSTRACT & COMMENTARY

By Michael Lin, MD, PhD

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Dr. Lin reports no financial relationships relevant to this field of study. This article originally appeared in the October 2012 issue of Neurology Alert.

Synopsis: *Biomarkers in the cerebrospinal fluid open the possibility of diagnosing early or even presymptomatic cases of Alzheimer's disease, thereby expanding the potential window for therapy.*

Sources: Bateman RJ, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 2012;367:795-804. Blennow K, et al. Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in patients with mild to moderate Alzheimer disease. *Arch Neurol* 2012;69:1002-1010. Roh JH, et al. Disruption of the sleep-wake cycle and diurnal fluctuation of beta-amyloid in mice with Alzheimer's disease pathology. *Sci Transl Med* 2012;4: 150ra122.

Revised guidelines for the diagnosis of alzheimer's disease (AD), published last year by the National Institute on Aging and the Alzheimer's Association, place new emphasis on laboratory and imaging biomarkers.[1,2,3] Use of such biomarkers could allow earlier diagnosis, when symptoms are not yet severe enough to meet clinical criteria for AD,[2] or possibly even before symptoms arise.[3] There is gathering consensus that earlier diagnosis may be critical for successful intervention, as damage already may be severe by the time symptoms appear. Three recent papers highlight this new emphasis on biomarkers.

Bateman and colleagues investigated the timing of various biomarker and clinical changes in patients with autosomal dominant familial AD. Patients with a dominantly inherited AD mutation develop AD with 100% penetrance, and the age of onset is typically consistent between generations. The investigators analyzed baseline biomarker and clinical data from 128 members of dominantly inherited AD pedigrees (88 carriers, 40 noncarriers), and they estimated the time from expected symptom onset based on the parent's age at symptom onset. A characteristic sequence of pathologic changes was found: 1) Cerbrospinal fluid (CSF) Aß42 levels declined as early as 25 years before expected symptom onset; 2) Parenchymal Aß deposition, assessed by PET imaging with Pittsburgh compound B (PiB), was detected 15 years before expected symptom onset. Increased CSF tau levels and hippocampal atrophy were also detected at this time; 3) Glucose hypometabolism and impairment on neuropsychologic memory testing were observed 10 years before expected symptom onset; 4) Decline on Mini-Mental State Exam was detected 5 years before expected symptom onset; 5) Diagnostic criteria for dementia were met 3 years after expected symptom onset. These results support the hypothesis of a characteristic pathophysiologic cascade beginning with changes in Aß, and potentially could form the basis of entry criteria for new trials.

Roh and colleagues investigated the relationship between Aß biomarkers and sleep. The authors had previously shown that synaptic activity induces secretion of Aß, and that Aß levels in brain interstitial fluid (ISF) fluctuate with the sleep/wake cycle. In the current work, they showed that in transgenic mice overexpressing mutant APP and presenilin 1, brain accumulation of Aß with aging is associated with both loss of the diurnal fluctuation in ISF Aß as well as impairment in sleep/wake cycling. Importantly, both the diurnal ISF Aß fluctuations and sleep/wake cycling remained normal if Aß accumulation was prevented by immunizing the mice against Aß. In normal human subjects, they found a similar diurnal fluctuation in CSF Aß concentrations, which was still present in patients who had dominantly inherited AD mutations but no parenchymal Aß deposits (assessed by PET imaging with PiB). In contrast, patients with dominantly inherited AD mutations and parenchymal Aß deposits (assessed by PET imaging with PiB) had loss of the normal diurnal CSF Aß fluctuations. These results suggest that brain Aß

accumulation affects both sleep and normal diurnal Aß metabolism, and could be improved by preventing such accumulation. These findings could potentially be highly relevant, given the frequency of sleep disturbance with both aging and AD.

Blennow and colleagues used CSF biomarkers (Aß, phosphotau, and total tau) to monitor response to therapy in two Phase 2, multicenter, randomized, placebo-controlled trials of bapineuzumab, a monoclonal antibody against Aß. Forty-six subjects with mild-to-moderate AD (27 on bapineuzumab, 19 on placebo) were examined over 1 year. Interestingly, there were no clear cut changes in CSF Aß levels compared to baseline. However, CSF phosphotau levels decreased significantly compared to baseline in the bapineuzumab group (-9.9 pg/mL, $P = 0.001$), and this change was significantly larger than that seen in the placebo group ($P = 0.03$). CSF total tau levels also decreased significantly compared to baseline in the bapineuzumab group (-72.3 pg/mL, $P = 0.03$), though the difference between this change and that seen in the placebo group was not quite significant ($P = 0.09$). Given previous evidence that tau pathology likely follows Aß changes, these results suggest that Aß-directed immunotherapy can have effects "downstream" in disease pathogenesis. Unfortunately, the Phase 3 trials of bapineuzumab failed to show benefit in any of the primary clinical endpoints.[4]

■ COMMENTARY

Further work is necessary. For example, the study of Bateman and colleagues on the sequence and timing of biomarker changes was cross-sectional, and results need to be verified by longitudinal follow-up studies. Also, it remains to be seen whether dominantly inherited AD, which accounts for < 1% of cases, is an accurate model for "sporadic" AD. Another important question is what biomarkers, if any, can be used to monitor response to therapy and correlate well with clinical improvement. One interpretation of recent failures in AD therapeutic trials is that it is already too late to intervene by the time symptoms have appeared. If this is true, the only way to intervene pre-symptomatically will be by having reliable biomarkers for the disease. This will clearly be an active area in the immediate future. ■

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Pharmacology Update

Enzalutamide Capsules (Xtandi®)

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

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

A NEW ANDROGEN RECEPTOR ANTAGONIST HAS BEEN APproved for the treatment of late-stage prostate cancer. Enzalutamide was approved 3 months ahead of schedule due to a priority review by the FDA. The drug is comarketed by Astellas Pharma and Medivation as Xtandi.

Indications

Enzalutamide is indicated for the treatment of metastatic castration-resistant prostate cancer in patients who have previously received docetaxel.[1]

Dosage

The recommended dose is 160 mg (4 × 40 mg) once daily without regard to meals.[1] The capsules should be swallowed whole. The dose should not be coadministered with a strong CYP2C8 inhibitor (e.g., gemfibrozil). If this is unavoidable, the dose should be reduced to 80 mg daily.

Enzalutamide is available as 40 mg capsules.

Potential Advantages

Enzalutamide prolonged survival in men with metastatic castration-resistant prostate cancer after treatment with chemotherapy (e.g., docetaxel).[1,2]

Potential Disadvantages

Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYPC19.[1] Concomitant administration of enzalutamide and substrates of these isoenzymes will reduce their systemic exposure and possibly their effectiveness. The most common adverse events associated with enzalutamide are fatigue, diarrhea,

hot flashes, musculoskeletal pain, and headache. Seizures were the most common adverse events resulting in treatment discontinuation (0.9% for enzalutamide vs 0% for placebo).[3] The frequency of fall-related injuries and grade 1 or 2 hallucinations was also higher vs placebo (4.6% vs 1.3%) and (1.6% vs 0.3%).

Comments

Enzalutamide and its major active metabolite, N-desmethyl enzalutamide, are competitive androgen inhibitors. These have been shown to induce prostate cancer cell death and decrease tumor volume in cancer xenograft models.[1] The efficacy and safety of enzalutamide has been evaluated in a Phase 3, randomized, placebo-controlled trial in patients with metastatic castration-resistant prostate cancer who received prior treatment with docetaxel.[1,2] Patients (n = 1199) were randomized at a 2:1 ratio to enzalutamide 160 mg daily (n = 800) or placebo (n = 399) and androgen deprivation therapy was continued in all patients. Treatment continued until disease progression, initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal of treatment. Disease progression was defined as radiographic progression, a skeletal-related event, or clinical progression. Approximately one-half of each group received glucocorticoids. The primary outcome was overall survival. Secondary endpoints included measure of response (50% reduction in PSA and soft-tissue response based on assessment of lesions and tumor burden using the RECIST criteria); quality-of-life scores (10-point improvement in FACT-P); and measure of progression for PSA, radiographic, and first skeletal-related event. Analyses were based on intent-to-treat analysis. Percent survival was 61.5% for enzalutamide and 46.9% for placebo (hazard ratio [95% confidence interval]; 0.63 [0.53, 0.75] $P <$ 0.0001). The median survival time was 18.4 months and 13.6 months, respectively. PSA response rate was 54% vs 2% and soft-tissue response rates were 29% vs 4% for enzalutamide and placebo, respectively. Median times to PSA progression (8.3 vs 3.0 months), radiographic progression-free survival (8.3 vs 2.9 months), and time to first skeletal-related event (16.7 vs 13.3 months) were statistically in favor of enzalutamide.[2] Quality-of-life response rate was 43% vs 18% ($P < 0.001$).

Clinical Implications

Enzalutamide prolonged survival for approximately 5 months. The number needed to treat to achieve this benefit is approximately 7. A clinical trial is currently recruiting patients to compare enzalutamide to bicalutamide in patients with recurrent prostate cancer who have serologic and/or radiographic disease progression despite primary androgen deprivation therapy.[4] ■

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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. **After careful evaluation of all of the published literature, Jukema and colleagues concluded that statin therapy:**
   a. is not infrequently associated with cognitive decline, especially in men.
   b. is associated with a small risk for the development of cancer.
   c. is not associated with a proven increased risk of cognitive decline.
   d. is not associated with an increased risk for the development of type 2 diabetes mellitus.

2. **Significant interruptions in warfarin therapy for stroke prevention in atrial fibrillation patients are:**
   a. uncommon.
   b. associated with increased thromboembolic events.
   c. associated with less bleeding.
   d. All of the above

3. **All of the following are true regarding cerebrospinal fluid (CSF) biomarkers and Alzheimer's disease (AD), *except* for:**
   a. CSF Aß42 levels decline in the CSF many years before symptoms are apparent in AD.
   b. CSF tau levels are increased in AD.
   c. PET imaging with Pittsburgh compound B is always diagnostic of AD.
   d. Hippocampal atrophy, determined by MRI, occurs before symptoms in AD.
   e. Sleep disorders are common in patients with AD.

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

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

Beta-Blocker Use in Situations Other than Just Post-MI

Source: Bangalore S, et al. *JAMA* 2012; 308:1340-1349.

Current standard-of-care management of post-myocardial infarction (MI) patients includes long-term use of a beta-blocker, unless otherwise contraindicated. The length of the leash on this concept is not long, however, as prospective data confirming benefits of beta-blockers post-MI are limited to just a few years. Since clinicians have not been given concrete advice about when to *stop* beta-blockers, most patients are kept on beta-blockers indefinitely. Perhaps our indecisiveness is bolstered by anxieties related to the potential consequences of beta-blocker withdrawal in persons with known coronary artery disease (CAD).

In the absence of data from a randomized, prospective, long-term trial, observational data may provide some clues about the relative benefit (or lack thereof) of beta-blockers in at-risk populations. To that end, Bangalore et al report on the outcomes of three different at-risk populations from a CAD registry: post-MI patients (n = 14,043), CAD patients without history of MI (n = 12,012), and patients with CAD risk factors but no known CAD (n = 18,653). Study subjects were enrolled in 2003-2004, and followed for approximately 4 years.

Beta-blocker use was not associated with improved outcomes in *any* of the three subgroups, even the one group we take for granted that there will be beneficial effects: the post-MI group. In the 1990s, the term "cardioprotective" was sometimes used in reference to beta-blockers. Although this may be true for the few short years immediately after an MI where older clinical trials have found a benefit, whether such benefits persist, or extend to other at-risk groups, remains to be determined. ■

Long-Term Sexual and Psychological Adverse Effects of Finasteride

Source: Irwig MS. *J Clin Psychiatry* 2012;73:1220-1223.

Cutaneous dihydrotestosterone is etiologically involved in the development of male pattern baldness. Since finasteride blocks the conversion from testosterone to dihydrotestosterone, it is commonly used to treat the disorder. Systemic alpha-reductase inhibitors like finasteride are occasionally associated with sexual side effects, but only recently has there been the suggestion that finasteride-associated sexual side effects might persist beyond the time treatment is administered. Additionally, recent FDA labeling changes have added depression as a recognized adverse effect of finasteride treatment. Although mechanisms to explain persistent adverse sexual effects are unclear, some animal data suggest persistent diminution in penile relaxation and contraction subsequent to finasteride.

From a population of young men (mean age 31 years) with male pattern baldness (n = 91), Irwig compared men who reported sexual dysfunction for at least 3 months after finasteride cessation to men with male pattern baldness who had not used finasteride. Outcomes of interest were depression scores and suicidal thoughts.

Depression, depressive symptoms, and suicidal thoughts were all substantially more common in the former finasteride users than controls. For example, 75% of former users had a Beck Depression Inventory Score of at least 14 (confirming depression) as opposed to 10% of controls. It is important that clinicians recognize the potential for enduring adverse sexual and psychological symptoms associated with finasteride. ■

Novel CV Risk Markers: How Much Cluck for the Buck?

Source: The Emerging Risk Factors Collaboration. *N Engl J Med* 2012;367:14: 1310-1320.

The c-reactive protein (CRP) debate has no end in sight. While traditional risk stratification tools like the Framingham Risk Score remain well established to distinguish high- and low-risk groups, the intermediate-risk group is the population in which further refinement in risk score might be helpful. Tools like CRP and fibrinogen, when applied to persons of intermediate Framingham risk, might help identify a subgroup that merits consideration for interventions like statins.

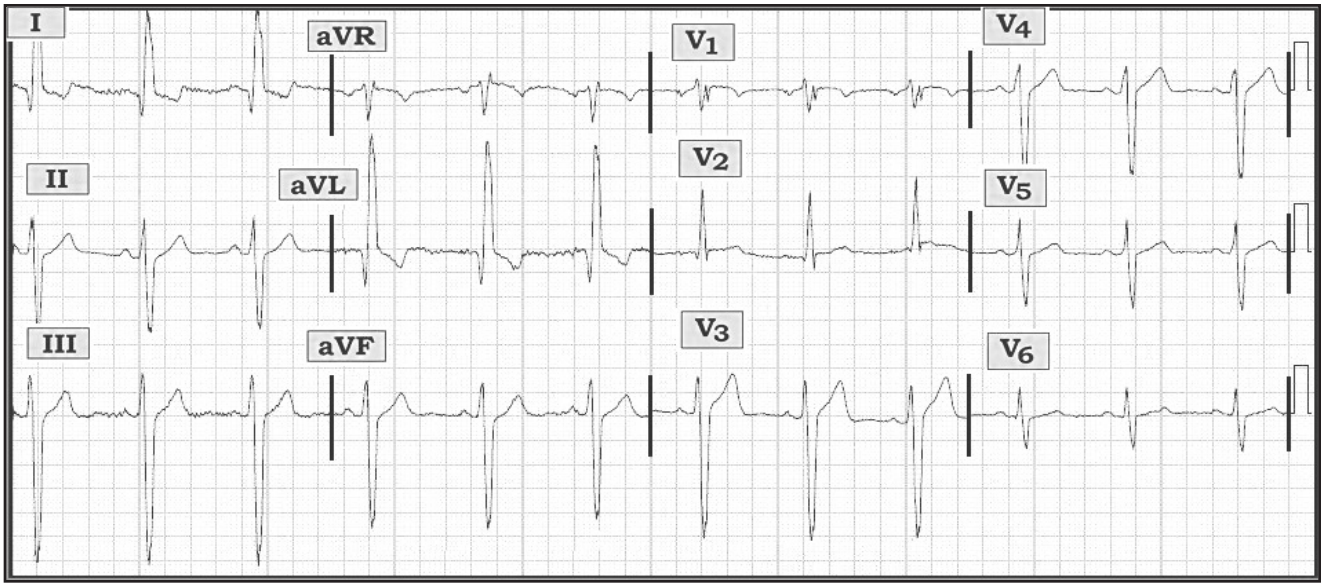
The Emerging Risk Factors Collaboration analyzed data from prospective cohort studies (n = 246,669) that included persons free of CV disease at baseline in whom CRP, fibrinogen, and components of Framingham risk score were available. Among persons with an intermediate Framingham risk score (10-20% risk of CV event over the next 10 years), the addition of either CRP or fibrinogen to risk assessment would result in reclassification of approximately 5% from intermediate to high risk. Such risk status elevation would justify statin treatment. According to current outcomes data, statin intervention in this population would prevent one CV event for every 440 intermediate-risk persons screened. Results were similar for fibrinogen.

The results obtained are "modeled" results rather than actual outcomes. CRP and fibrinogen testing are readily available. Yet, the number needed to test for avoidance of one CV event — more than 400 — is substantial. The authors do not offer an opinion on the *propriety* of such an investigation as CRP or fibrinogen; rather, they simply provide a metric to help quantify how much cluck for the buck one might anticipate. ■

ECG from a 22-year-old Man in a Wheelchair

By Ken Grauer, MD, *Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.



Scenario: The ECG shown above was obtained from a 22-year-old man in a wheelchair. How would you interpret the tracing? Can you think of a condition that might account for this clinical scenario?

Interpretation: The ECG shows sinus rhythm at about 70/minute. The PR interval is normal, but the QRS is prolonged to at least 0.12 second. QRS morphology in the three key leads (I, V1, V6) is not consistent with either left or right bundle branch block. Therefore, we would classify the conduction defect as *nonspecific* interventricular conduction delay (IVCD).

Continuing with the interpretation, we note marked left axis deviation consistent with left anterior hemiblock. QRS amplitude is markedly increased in lead aVL, although reliability of the ECG diagnosis of left ventricular hypertrophy (LVH) is reduced in the presence of conduction defects.

Regarding QRST changes, there are deep and wide Q waves in the high lateral leads (I, aVL). In addition, there is a small Q wave in lead V2. QRS morphology in lead V1 is peculiar, as there is an rSr's' complex. This is followed by abrupt transition by lead V2 in which a disproportionately tall R wave is noted. R wave amplitude drops off by lead V3, with persistent S waves seen throughout the remaining precordial leads. There is ST segment depression in lateral leads I and aVL, which may reflect "strain" from suspected LVH. That said, ST-T wave changes do not appear to be acute.

Our overall impression is that this ECG is clearly abnormal and highly unusual for a young adult. Given the history of a "22-year-old man in a wheelchair" should suggest the possibility of a cardiomyopathy such as Duchenne Muscular Dystrophy (DMD). There are more than 20 different genetic forms of muscular dystrophy, of which DMD is the most common of these rare disorders. DMD is almost exclusively seen in males, with unfortunate outcome of progressive muscle deterioration and weakness that invariably leads to death at an early age. Cardiac involvement is the rule, with the most common ECG abnormalities in DMD and other muscular dystrophies being QRS widening from conduction defects (usually nonspecific IVCD); abnormal Q waves not due to infarction (especially in lateral leads); and a polyphasic rSr's' in lead V1 with surprisingly tall anterior precordial R waves. All of these features are seen in this case.

For more information on this ECG Review and DMD, please visit: https://www.kg-ekgpress.com/ecg_-_duchenne_musc_dystrophy/. ■

In Future Issues:

Statins and Fatigue

PHARMACOLOGY WATCH

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

Do Benzodiazepines Cause Dementia in the Elderly?

In this issue: Dementia and benzodiazepines; effectiveness of omega-3 fatty acid and *Ginkgo biloba* supplements; and FDA actions.

Benzodiazepines and dementia

Can benzodiazepines increase the risk for dementia? Researchers in France studied 1063 men and women with an average age of 78 who were free of dementia and did not start taking benzodiazepines until they had been followed for at least 3 years. During a 15-year follow-up, 253 cases of dementia were confirmed. New use of benzodiazepines occurred in 9% of the study population and was associated with an increased risk of dementia (32% benzodiazepine group vs 23%, adjusted hazard ratio 1.60, 95% confidence interval [CI] 1.08-2.38). After correcting for the existence of depressive symptoms as well as age and diabetes, the hazard ratio was unchanged. A secondary analysis looking at participants who started benzodiazepines at different times during follow-up also showed an elevated risk of dementia. Results of the complementary, nested, case-control study showed that ever use of benzodiazepines was associated with an approximate 50% increased risk of dementia compared with never users. The authors conclude that in this prospective, population-based study new use of benzodiazepines was associated with a significantly increased risk of dementia. They further conclude that "indiscriminate widespread use should be cautioned against" (*BMJ* 2012;345:e6231). The obvious criticism of the study was the presence of confounders — whether use of benzodiazepines was a marker for early onset dementia rather than a cause. While the authors feel the study was carefully controlled, selection bias cannot be completely ruled out. They further state that the research should be done on younger patients to see if starting benzodiazepines at ages younger than 65 may have deleterious effects. They also recommend that "physicians and regulatory agencies should consider the increasing evidence of potential adverse effects of this drug class for the general population." ■

Popular supplements' use questioned

Two popular supplements — omega-3 fatty acids and *Ginkgo biloba* — may be of limited value, according to two recent studies. Omega-3 fatty acids are thought to have a number of benefits, including lowering triglyceride levels, preventing arrhythmias, decreasing platelet aggregation, and lowering blood pressure. But the fish oil supplement's ability to prevent major cardiovascular events has been debated in the literature. Twenty studies of nearly 67,000 patients were included in a meta-analysis looking at the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke. After correcting for dose and comorbidities, there was no difference in the absolute or relative risk of any of the outcomes associated with omega-3 supplementation. The authors concluded that marine-derived omega-3 polyunsaturated fatty

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acid supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (*JAMA* 2012;308:1024-1033).

Ginkgo biloba for the prevention of Alzheimer's disease (AD) was studied in a randomized, parallel group, double-blind, placebo-controlled trial of adults age 70 years or older who spontaneously reported memory complaints to their primary care physician in France. Patients were randomized to a twice per day 120 mg standardized *Ginkgo biloba* extract or matching placebo and followed for 5 years. The primary outcome was conversion to probable AD. More than 2800 patients were enrolled with about 1400 patients in each group. By 5 years, 61 participants in the ginkgo group were diagnosed with AD vs 73 in the placebo group (hazard ratio 0.84, 95% CI 0.60-1.18; $P = 0.306$). Adverse events were the same between both groups and mortality was roughly the same as well. Sixty-five participants in the ginkgo group had a stroke compared to 60 in the placebo group ($P = 0.57$). The authors conclude that long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to AD compared to placebo (*Lancet Neurology* 2012;11:851-859). ■

FDA actions

The FDA has approved teriflunomide for the treatment of relapsing forms of multiple sclerosis (MS). The approval was based on a 2-year study in which the drug reduced relapses by nearly a third compared to placebo — results that are about the same as other MS drugs and no better than Merck's popular injectable interferon beta 1a (Rebif). Side effects include diarrhea, abnormal liver function tests, nausea, and hair loss. It should not be used during pregnancy. Teriflunomide has the advantage of being a once-daily oral medication, the second oral MS medication after Novartis' fingolimod (Gilenya). Teriflunomide will be marketed by Sanofi Aventis as Aubagio. A third oral MS medication, Biogen Idec's BG-12, was recently found to reduce MS relapses by about 50% (*N Engl J Med* 2012;367:1087-1097; 1098-1107). BG-12 is not yet approved by the FDA, but a decision is expected before the end of the year.

The FDA has delayed the approval of apixaban (Eliquis) once again. Pfizer and Bristol-Myers Squibb's novel oral anticoagulant (NOAC) was expected to be approved last spring after publication of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which showed that the drug was effective in preventing strokes in patients with non-valvular atrial fibrillation — data that suggested that the drug was perhaps even more effective than the two other NOACs, dabigatran (Pradaxa) and rivaroxaban (Xarelto). In June, the FDA told the manufacturers they needed "additional information on data management and verification from the ARISTOTLE trial." Now, the agency says that the review date will be March 17, 2013. No reason was given by the FDA for the delay.

About 25% of Internet consumers have purchased prescription medications online, while at the same time, the prevalence of fraudulent Internet pharmacies has grown. The FDA has now launched a national campaign to raise public awareness called BeSafeRx – Know Your Online Pharmacy, a resource that provides patients and caregivers with a better understanding of who they are buying from, and makes sure the medication they buy matches what their doctor prescribed. The FDA recommends that patients only buy medications from online pharmacies that require a prescription, are located in the United States, have a licensed pharmacist available for consultation, and are licensed by the patient's state board of pharmacy. More information can be found at www.FDA.gov/BeSafeRx.

The FDA has approved enzalutamide to treat men with late-stage, castration-resistant prostate cancer under the agency's priority review program. The drug was approved based on a study of nearly 2000 men with metastatic prostate cancer who had been previously treated with docetaxel. Men treated with enzalutamide lived an average of 18.4 months vs 13.6 months for men treated with placebo. Enzalutamide is co-marketed by Astellas and Medivation as Xtandi.

The FDA has also approved a new agent for the treatment of advanced colorectal cancer. Regorafenib is a multi-kinase inhibitor that was also approved under the FDA's priority review program. In a study of 760 patients with previously treated metastatic colorectal cancer, regorafenib extended survival about 45 days to 6.4 months from 5 months for placebo as well as progression-free survival of 2 months vs 1.7 months for placebo. Regorafenib is marketed by Bayer as Stivarga. ■