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INSIDE

How Do You Rate Urate?

ABSTRACT & COMMENTARY

Synopsis: *Elevated serum uric acid is a marker for cardiovascular mortality.*

Source: Niskanen LK, et al. *Arch Intern Med*. 2004;164:1546-1551.

Analyzing data from the Kuopio Ischaemic Heart Disease Risk Factor Study, Niskanen and colleagues looked for associations between serum uric acid (SUA) and risk factors for cardiovascular and all-cause mortality. The Kuopio study was a prospective, population-based inquiry that followed 2682 Finnish men who were 42, 48, 54, and 60 years old at baseline between 1984 and 1989. Follow-up (mean, 11.9 years) was through 1998. The current study excluded men with cardiovascular disease (except hypertension), cancer, or diabetes mellitus and men with missing SUA levels, leaving 1423 subjects. During follow-up, there were 157 deaths (55 from cardiovascular disease [CVD]). Age, smoking, alcohol intake, low socioeconomic status, hypertension, and body mass index were all associated with CVD death in univariate analysis. Age, smoking, alcohol intake, low socioeconomic status, use of hypertensive medications, and waist circumference were all associated with all-cause mortality. SUA was associated with CVD death and showed a trend to all-cause mortality. There was a "dose-response" effect with age-adjusted proportional hazards analysis showing a 2.7-fold increase when comparing the lowest tertile with the upper two. Adjusting for factors related with gout or metabolic syndrome did not weaken the association.

COMMENT BY ALLAN J. WILKE, MD

The strengths of this study are its prospective design, long follow-up, and the exclusion of significantly ill men.

Uric acid is a byproduct of purine. Hyperuricemia can result from increased purine intake, purine overproduction, increased purine breakdown, or impaired urate excretion by the kidneys. Such a variety of mechanisms makes it difficult to ascribe a causative role in CVD to SUA. A recent study of Korean men did not find that SUA is an independent risk factor for death from cancer, atherosclerotic CVD, or all causes,[1] nor was this the case

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among community-dwelling elderly patients in the United States.[2] However, among men and women with known coronary artery disease, SUA was an independent predictor of mortality.[3] The National Health and Nutrition Examination Survey epidemiologic follow-up study also found SUA to be an independent risk for cardiovascular death.[4] Is SUA an evildoer or an innocent bystander in CVD? This question is yet to be answered. More practically, does treatment of elevated SUA reduce CVD risk? Until recently, there was no evidence for that. This may be changing. The Losartan Intervention for End Point reduction in hypertension study showed that losartan was superior to atenolol in reducing CVD morbidity and mortality, and it reduced the increase in SUA better than atenolol, which appeared to account for 29% of the treatment effect.[5]

Assuming that you can extrapolate these findings from a group of middle-aged male Finns to your next patient with an elevated SUA, what are you going to do? At the very least, keeping a high index of suspicion for possible cardiovascular disease is in order. ■

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EDITORIAL GROUP HEAD: Lee Landenberger.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

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Abdominal Aortic Aneurysm

ABSTRACT & COMMENTARY

Synopsis: *Annual, or less frequent, surveillance intervals are effective for aneurysms < 45 mm in diameter.*

Source: Brady AR, et al. Abdominal Aortic Aneurysm Expansion: Risk Factors and Time Intervals for Surveillance. *Circulation*. 2004;110:16-21.

Studies have shown that abdominal aortic aneurysms (AAA) can be safely followed until a diameter of 55 mm is reached before considering surgery. However, the size surveillance frequency is poorly understood. Thus, Brady and colleagues, from the United Kingdom (UK) Small Aneurysm Trial, analyzed repeated AAA diameter measurements by ultrasonography from a large national cohort to characterize AAA expansion and its determinants. In 93 UK hospitals, patients referred to vascular surgeons with aneurysms 40 to 50 mm in diameter, who were fit for surgery, were asked to participate in a trial comparing immediate surgery to surveillance and surgery, if the aneurysm became > 55 mm, grew by > 10 mm/year, or they had symptoms due to the aneurysm. The surveillance frequency was every 3 months for aneurysms > 50 and < 55, and 6 months for those < 50 mm. Sophisticated, statistical methods were used to eliminate bias.

Among 2366 patients recruited, 1743 had more than 1 (9125 total) AAA diameter measurement over a mean of 2 years follow-up (maximum 8 years). The mean, initial AAA diameter was 43 mm, and the

growth rate was 2.6 mm/year (95% range, 1.0-6.1 mm/year). The strongest predictor of growth rate was initial size. Growth rates were lower in diabetics and those with peripheral vascular disease, but higher in current smokers. Age, hypertension, and other cardiovascular disease risk factors were not related to growth. The surveillance intervals to keep < 1% at 55 mm were 36, 24, 12, and 3 months for aneurysms of 35, 40, 45, and 50 mm, respectively. Brady and colleagues concluded that annual, or less frequent, surveillance intervals are effective for aneurysms < 45 mm in diameter.

COMMENT BY MICHAEL H. CRAWFORD, MD

This study presents highly practical information that is of value to patients, physicians, and health care systems. Brady et al set the goal of keeping the discovery of patients with AAA diameter > 55 mm to 1% as their surveillance interval standard. This should be acceptable to all. They found that the growth rate of AAAs was slower than appreciated in previous studies because the earlier studies used linear regression modeling, which is biased toward larger aneurysms with higher growth rates. AAA size is the major factor in predicting aneurysm growth rates. Thus, the surveillance frequency proposed varies with initial AAA size.

Since the upper limit of the abdominal aortic diameter is 30 mm, why not operate on everyone above that limit and save the cost of all this screening? Two studies, 1 in the United States, and this study from the United Kingdom, did not show a mortality benefit of such a strategy. However, some studies have shown a low rupture rate up to a diameter of 60 mm. Thus some have recommended advising surgery based upon AAA size and the risk of surgery. For example, a healthy 60-year-old with an aneurysm of 55 mm would get surgery, but in a more risky patient, one might wait until 60 or 65 mm. This approach makes some sense, but has not been studied prospectively.

Interestingly, traditional atherosclerosis risk factors do not seem to be a factor in aneurysm growth, with the exception of smoking. However, the effect of smoking on AAAs may not be related to its effect on atherosclerosis. Pathologic studies have shown that AAAs are not typically atherosclerotic, and the main findings are inflammation and proteolysis. Thus, we don't fully understand the pathogenesis of AAAs, but smoking cessation would make sense since it increases the growth rate of AAAs by up to 20%. Because we don't understand the pathogenesis of AAAs, some have suggested that every 70-year-old man should have 1 abdominal ultrasound screening or other imaging study. The effectiveness of this recommendation is not proven, but it makes some sense. We are not told how the patients in this study were identified. Some may have had symptoms, a positive abdominal physical exam, or routine screening.

Again, because of our ignorance about the pathogenesis of AAA, Brady et al have suggested that surveillance be applied to post-stent graft and post-operative patients, under the theory that the untreated segments of aorta may expand over time and cause leaks. ■

Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology, University of California ,San Francisco.

On-Demand Rabeprazole 10 mg Maintains Symptom Relief in Patients with Non-Erosive Reflux Disease

ABSTRACT & COMMENTARY

Synopsis: *In patients with symptomatic nonerosive reflux disease, intermittent on-demand therapy with the PPI rabeprazole provided good symptom control with tablets taken on average approximately 1 day out of 4.*

Source: Bytzer P, et al. *Alimentary Pharmacology & Therapeutics*. 2004;20:181-188.

Gastroesophageal reflux disease (GERD) is extremely common, but at least 50-70% of patients with GERD symptoms have normal esophageal mucosa on endoscopy. Despite physicians' assumptions to the contrary, compliance studies strongly suggest that patients with reflux symptoms generally only take their medications while actually experiencing reflux-related symptoms. This nonerosive reflux disease (NERD) study was undertaken to assess the on-demand efficacy of rabeprazole (a PPI noted for relatively rapid onset of profound acid suppression). Five hundred thirty-five NERD patients with = 3 d/wk of baseline moderate-to-severe heartburn were enrolled (numbers based on power calculations).

All patients took rabeprazole 10 mg daily for 4 weeks. Thereafter, patients were randomized to either rabeprazole 10 mg or placebo (2:1 allocation), taken

one tablet daily at heartburn onset and continued daily before breakfast until 24 hours without heartburn had transpired. Maalox was available for breakthrough symptoms. Twenty percent of placebo recipients withdrew from the study vs 6% of rabeprazole recipients. Symptom relief occurred significantly earlier with rabeprazole than with placebo. Rabeprazole was taken on 26% of possible days. Rabeprazole and placebo were both well tolerated. Bytzer and associates speculate that on demand therapy may have an important role in management of NERD and that such treatment would provide substantial cost savings vs continuous PPI therapy as has been traditionally prescribed.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

This paper joins other similar studies of several other PPIs in the management of NERD. There seems to be little doubt that on-demand treatment could be clinically acceptable and economically advantageous in this setting. Although these studies have not addressed the absolute long-term safety of intermittent NERD therapy, existing information suggests that there should be no major difficulties with adoption of such regimens. That is, it seems unlikely that intermittently treated NERD patients would nonetheless develop significant mucosal injury, Barrett's esophagus, or esophageal adenocarcinoma.

Ideally, of course, some prospective long-term investigations should be undertaken to verify the correctness of this hypothesis. The real question surrounds the possible dangers of using such intermittent therapy in uninvestigated GERD patients, some of whom might have significant esophageal mucosal abnormalities. Although no scientific data exist to completely answer this conundrum, it seems likely (at least to Bytzer et al) that intermittent PPI therapy might be quite satisfactory for GERD patients with lesser grades of esophageal damage (eg, tiny erosions at the squamocolumnar junction). It seems quite unlikely that mild esophagitis would progress in previously symptomatic patients whose symptoms are adequately controlled with intermittent therapy. However, this mild erosive GERD subgroup certainly should be prospectively studied before on-demand therapy is promoted in GERD patients who have not been evaluated by endoscopy. In this era of rapidly rising medical costs, the benefits of on demand PPI therapy certainly warrant careful consideration. ■

We Can Improve the Treatment of Patients with Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *Angiotensin-converting enzyme inhibitors decreased the number of defibrillation attempts needed and reduced hospitalization in patients with atrial fibrillation.*

Source: Zaman A G et al. *Am Heart J*. 2004;147:823-827.

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a high risk of thromboembolism. A recent Framingham study demonstrated that men and women, at age 40, had a 1 in 4 lifetime risk for developing AF.[1] The best therapy for AF is still uncertain. Rate-controlled therapy when compared to rhythm-controlled therapy has recently been shown to decrease mortality.[2] Little is known about the long term outcome of nonpharmacologic therapies such as atrioventricular nodal ablation, pacemakers and atrial defibrillators.[3]

Zaman and colleagues have noted that withdrawal of angiotensin-converting enzyme inhibitors (ACEI) was associated with AF in patients undergoing coronary artery bypass surgery. As a result of this finding they set out to establish whether ACEI could reduce atrial arrhythmogenicity.

The study was a 1 year, prospective, follow-up, comprised 47 patients with persistent AF undergoing electrical cardioversion. Patients receiving ACEI were compared with those receiving other medications. The study end point was the number of defibrillation attempts required for atrial defibrillation and the number of hospital admissions. A secondary end point was change in signal-averaged P-wave duration (SAPD) 1 year after successful electrical cardioversion. (Signal-averaged electrocardiography reflects conduction abnormalities in the perinodal atrial muscle. Remodeling of the atrial myocardium may be detected by prolongation of the atrial impulses).[4]

Of those admitted and requiring defibrillation, the number of defibrillation attempts required for successful cardioversion was significantly less in the ACEI group. The incidence rate ratio for admissions, comparing recipients of ACEI with those not receiving ACEI, was 0.14. Patients receiving ACEI therapy had significantly lower SAPD at 1 year when compared with the no-ACEI group.

The use of long-term ACEI therapy facilitated electrical defibrillation in patients with persistent AF. ACEI therapy also reduced SAPD, suggesting amelioration of the arrhythmogenic substrate. Furthermore, they confirmed that SAPD is prolonged in patients with persistent AF.

COMMENT BY RALPH R. HALL, MD, FACP

Zaman et al point out that the observational nature of this study and the small number of patients are potential limitations. Also the majority of the patients in this study were hypertensive so the study might not apply to those with normal blood pressure. They also note that the non-randomized nature of this study led to differences in the medication the 2 groups were receiving. However, there is no evidence to suggest that beta blockers or calcium antagonists affect AF. The study did not include measurements of diastolic dysfunction. This is another factor which should be examined. AF occurs in a high percentage of patients with diastolic dysfunction.

Consider the patient who has had 5 bouts of AF, all of short duration. All episodes occurred while on decongestants and all were more than a year apart. Repeated 48 hour monitoring did not identify asymptomatic AF. Will he eventually have more protracted episodes? Will taking ACEI prevent recurrence?

There is a need for more and improved trials for patients with AF. Treatment for AF is often unsatisfactory and many of the patients we see do not fit the profiles of those in previous trials. Therefore, despite the limitations of this study, it identifies the need for randomized trials to examine the role of ACEI in the management and perhaps prevention of atrial fibrillation. ■

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Pharmacology Update

Ezetimibe and Simvastatin Tablets (Vytorin)

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

The FDA has approved the combination of ezetimibe and simvastatin for the treatment of hypercholesterolemia. This combination product provides different mechanisms of action for lowering cholesterol. Simvastatin is a widely used HMG-CoA reductase inhibitor and ezetimibe inhibits the absorption of cholesterol. The product is marketed by Merck/Schering-Plough as Vytorin.

Indications

Ezetimibe/simvastatin is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL-C, Apo B, triglycerides and non-HDL-C and to increase HDL-C in patients with primary hypercholesterolemia or mixed hyperlipidemia. It is also indicated for the reduction of elevated total and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid lowering treatments.[1]

Dosage

The usual recommended starting dose is 10 mg ezetimibe and 20 mg of simvastatin. The dose may range from 10 mg/10 mg to 10 mg/80 mg depending on the level of cholesterol reduction needed. No dosage adjustment is necessary in patients with mild or moderate renal dysfunction or mild hepatic dysfunction.[1]

Ezetimibe/simvastatin is supplied in 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg tablets.

Potential Advantages

The combination product provides dual and complementary mechanisms for reducing cholesterol levels. Ezetimibe inhibits cholesterol absorption while simvastatin inhibits cholesterol synthesis. This combination is more effective than simvastatin alone.[2] Statin-associated myopathy is dose related, and the combination achieves LDL reduction goals with a lower statin dose, thus reducing the risk of myopathy. The combination of ezetimibe/simvastatin produced greater LDL-C reduction and HDL-C increase than atorvastatin.[3]

Potential Disadvantages

The frequency of elevated ALT/AST (3 x upper limit of normal) appears to be higher with ezetimibe/simvastatin compared to simvastatin monotherapy.[2,4] The experience of ezetimibe in non-Caucasians is limited.[1] The long-term safety and effectiveness of ezetimibe has not been established.

Comments

The combination of ezetimibe and simvastatin provides dual complementary mechanisms for lowering cholesterol. The reduction in LDL-C change from untreated baseline ranged from -45% to -60% for the

10 mg/10 mg to 10 mg/80 mg.[1] The addition of ezetimibe to statin monotherapy results in about an additional 25% reduction in LDL-C.[4] In clinical studies, patients who received ezetimibe/simvastatin overall achieved significantly lower decrease in LDL-C, total cholesterol, ApoB, triglyceride, and non HDL-C. The combination also resulted in incremental decrease in high-sensitivity C-reactive protein.[5] Ezetimibe does not appear to add to the increase in HDL-C.[1] At maximum dose ezetimibe/simvastatin (10 mg/80 mg) reduced LDL-C by 59.4% compared to 52.5% for atorvastatin 80 mg ($P < 0.001$). HDL-C was increased by 12.3% compared to 6.5% respectively ($P < 0.001$).[3] The combination is well tolerated and does not appear to result in increase risk of myopathy/rhabdomyolysis. However the combination may lead to a higher incidence of elevation of ALT/AST at 3 x upper limit of normal. The wholesale cost for ezetimibe/simvastatin is $2.34 per day for all strengths. The cost for atorvastatin (20 mg to 80 mg) is $3 per day.

Clinical Implications

The combination of ezetimibe and simvastatin provides another option for lowering of LDL-C and non HDL-C. This is particularly valuable for patients who cannot tolerate high dose statin therapy. Given the finding from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) and the new LDL goals for patients at high risk for cardiovascular events, combination with complementary mechanisms may be useful in selected patients. ■

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CME Questions

10. Which of the following statements are true?

a. The lifetime risk of a 40-year-old male or female for developing AF is 1 in 4.
b. The effects of ACEI in patients with diastolic dysfunction have been well documented.
c. ACEI prolonged signal-averaged P-wave duration.
d. ACEI shortened signal-averaged P-wave duration.
e. both a and d are correct

11. In the Kuopio Study, serum uric acid predicted death from:

a. all causes.
b. cardiovascular disease.
c. cancer.
d. diabetes mellitus.

12. Which statement below is best justified?

a. Patients with severe esophagitis and Barrett's esophagus would be excellent candidates for on-demand PPI therapy.
b. On-demand PPI treatment could be considered in GERD patients with laryngitis, noncardiac chest pain, and GERD-exacerbated asthma.
c. Non-erosive reflux disease (NERD) documented by endoscopy would be the ideal setting for consideration of on-demand PPI therapy.
d. There is substantial risk that even NERD could ultimately progress to Barrett's esophagus and esophageal adenocarcinoma.
e. Excellent data already exist to describe the natural history of mild to moderate erosive esophagitis, including some level of progression to severe esophagitis and its complications.

Answers: 10 (e); 11 (b); 12 (c)

By Louis Kuritzky, MD

Effect of the Dietary Approaches to Stop Hypertension Diet and Reduced Sodium Intake on Blood Pressure Control

The dietary approaches to stop Hypertension (DASH) diet, which suggests high intake of fruits, vegetables, and low-fat diary products, has been shown to favorably affect blood pressure in Stage 1 Hypertension (140-159/90-99) as well as pre-hypertension (130-39/85-89). A reduced sodium intake diet (RSI) has also been shown to have beneficial BP effects in these groups. Whether the combination would provide additive benefits was the subject of this trial. Subjects (n = 412) were randomly allocated to DASH or control diets with high (142 mmoL/d), intermediate (107 mmoL/d), or low (65 mmoL/d) sodium content. Study subjects ate the DASH (or control) diet for 3 consecutive 30 day intervals, each interval with a different sodium content. To ensure compliance and consistency, all meals were provided by Svetky and colleagues.

Adding sodium restriction to the DASH diet resulted in a 2-2.6 fold greater likelihood of BP being controlled. At the lowest sodium intake, 84% of hypertensive patients achieved BP control (< 140/90). In persons with isolated systolic hypertension, the pattern of responsivity was similar. In persons with high-normal BP, 76% were restored to normotension with DASH+RSI. Application of these dietary modulations has meaningful beneficial effects, and may obviate or reduce the need for pharmacotherapy. ■

Svetkey LP, et al. J Clin Hypertens. 2004;6:373-381.

Methylprednisolone, Valacyclovir, or the Combination for Vestibular Neuritis

Vestibular neuritis (VN) is characterized by acute onset of vertigo, a positive Romberg's sign, nystagmus, and nausea. It is second only to benign paroxysmal positional vertigo as a cause of peripheral vestibular vertigo. The most popularly favored putative cause of VN is herpes simplex virus, although other etiologic explanations (like vestibular ischemia) are also suggested. Full vestibular recovery from VN occurs in less than half of cases, leaving patients with deficits such as postural imbalance during walking.

Corticosteroids, antiviral agents, or both are sometimes used to treat VN, but little evidence exists to confirm or disprove the efficacy of such interventions. This study compared methylprednisolone (MPD), valacyclovir (VAL), the combination (MPD + VAL) and placebo in subjects (n = 141) with acute VN of less than 3 days duration. MPD was administered orally QAM for 22 days, titrated 100 mg daily down to 10 mg. VAL was dosed 500 mg t.i.d. orally for 7 days.

At 12-month followup, the improvements in vestibular paresis ranged from 36.0% (VAL) to 39.6% (placebo), 59.2% (MPD + VAL), and 62.4% (MPD). These data do support the beneficial effects of corticosteroids, but do not support efficacy of VAL in VN. Although it is possible, and data in herpes encephalitis supports this concept, that VAL was not administered early enough in the disease process to have a favorable impact, since patients were seen within the first 72 hours of disease, it is unlikely that clinicians will be provided any opportunity for earlier drug administration. ■

Strupp M, et al. N Engl J Med. 2004; 351:354-361.

Improved Plasma Glucose Control, Whole-Body Glucose Utilizations, and Lipid Profile on a Low-Glycemic Index Diet in Type 2 Diabetic Men

At the same level of grams of carbohydrate, different foods vary in their rate of rise of plasma glucose, and in the subsequent amount and timing of insulin response they elicit. In theory, consumption of foods with a favorable (ie, low) glycemic index should favorably affect diabetic control. To date, there have been insufficient data to confirm or refute the role of a dietary choices based upon glycemic index. Supporting the role of a low glycemic index diet (LGI) are data that indicate better A1c levels and reduced fat mass, even in the absence of a measurable effect upon plasma glucose.

Rizkalla et al studied diabetic men (n = 12) who were administered a LGI diet vs a high glycemic index diet for 4 weeks, followed by a 4 week washout and then crossover to the other diet.

Numerous statistically significant favorable changes occurred during the LGI phase, including impact on fasting glucose, A1c, glucose use, LDL, plasma fatty acids, and even fibrinolysis status, as indicated by plasminogen activator inhibitor activity. If these effects are sustainable, they could have important positive long-term effects on diabetes. ■

Rizkalla SW, et al. Diabetes Care. 2004;27:1866-1872.

Healthy Patient/Many Findings

By Ken Grauer, MD

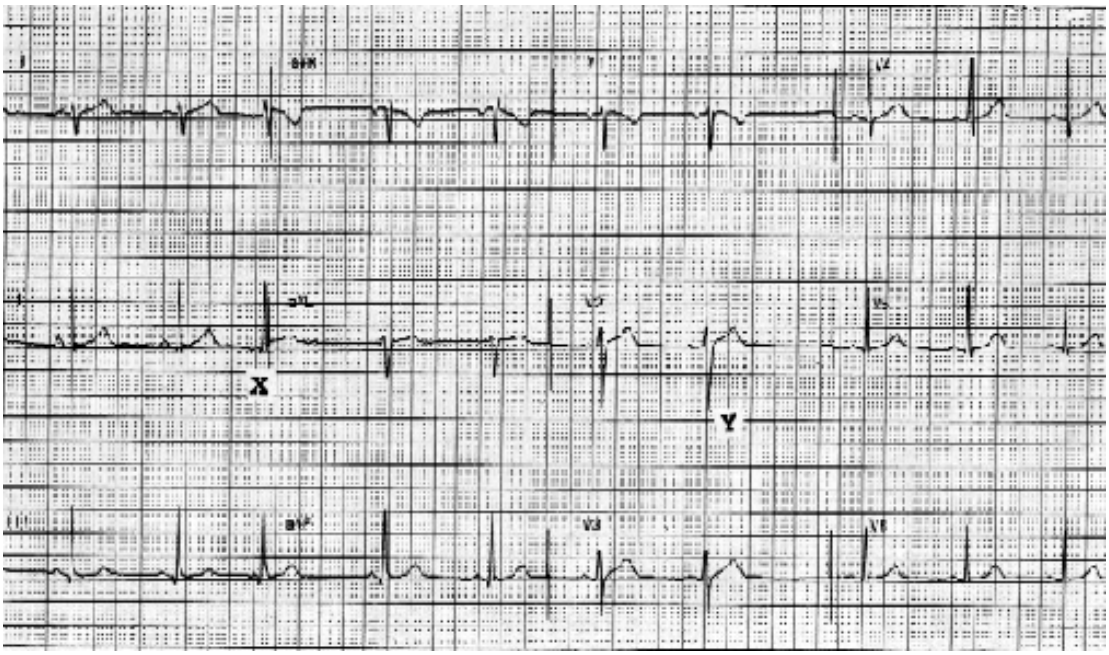

Figure. 12-lead ECG obtained from a healthy, asymptomatic 42-year-old man. How many findings can you identify?

Clinical Scenario: The ECG in the Figure was obtained from a healthy, asymptomatic 42 year old man. This ECG was done as part of his routine insurance physical examination. How many ECG findings can you identify on this tracing? Given the above scenario, are any of these findings likely to be of clinical significance?

Interpretation/Answer: The underlying rhythm in this tracing is sinus. Two PACs (premature atrial contractions) are seen: beats X and Y. The first PAC (beat X) manifests a different P wave morphology (it is of small amplitude and biphasic). It conducts normally. The second PAC *follows* the QRS complex labeled Y, and is identified as a subtle notching of the T wave in lead V_1 and slight peaking of the T wave in leads V_2 and V_3. Support that these admittedly subtle alterations in T wave morphology truly reflect a hidden PAC is forthcoming from the relative pause in the rhythm following beat Y. Thus, this second PAC that occurs much earlier in the cycle than the first PAC is "blocked" (ie, not conducted to the ventricles).

The other ECG findings on this tracing include RAD (right axis deviation), small septal q waves in the inferolateral leads, an rSr' pattern in lead V_1, and slight J point ST segment elevation with subtle J point notching in the lateral precordial leads as well as lead II.

Clinical correlation is the key to interpreting the likely significance of the ECG findings seen here. One should inquire if the patient is aware of the "skipped beats" (ie, PACs) seen here, and if potential causes may exist (ie, caffeine consumption or stimulant medications). RAD and the rSr' in lead V_1 are commonly seen normal variants in otherwise healthy young adults, but one should be sure there is no right-sided heart murmur or other evidence of pulmonary or valvular disease. J point ST segment elevation and notching almost certainly reflects a normal variant early repolarization pattern in this asymptomatic patient without any history or symptoms of pericarditis or ischemia. ■

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

New Clinical Guidelines on Cholesterol Management

The National Cholesterol Education Program (NCEP), a product of a collaboration of the National Heart, Lung, and Blood Institutes, the American College of Cardiology, and the American Heart Association, has updated its clinical practice guideline on cholesterol management. Based on several recent studies, that suggest that aggressive lowering of LDL cholesterol benefits high-risk patients, the new guidelines recommend aggressive treatment for patients who are at risk for coronary artery disease. Specifically, patients who are defined as "very high-risk" should be considered for aggressive treatment. Very high-risk patients are defined as those who have cardiovascular disease together with multiple risk factors (especially diabetes), severe and poorly controlled risk factors (such as continued smoking), or metabolic syndrome. The guideline had previously recommended drug therapy in these patients only if the LDL cholesterol was greater than 130 mg/dL, with a goal of 100 mg/dL. The new guideline recommends a treatment threshold of 100 mg/dL, with a goal of 70 mg/dL. "High-risk patients" are defined as those who have coronary heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, or 2 or more risk factors (such as smoking or hypertension) that give a greater than 20% chance of having heart attack within 10 years. The LDL goal for these patients remains 100 mg/dL or less, and the new guideline now recommends drug treatment for those high-risk patients with an LDL > 100 mg/dL. Moderately high-risk patients are defined as those with 2 or more risk factors for coronary heart disease and a 10-20% risk of heart attack within 10 years. For these patients, drug therapy is recommended to lower LDL cholesterol under 130 mg/dL, and the option is given to treat to levels under 100 kg/dL. For lower-risk patients, the guideline was not changed. Drug therapies recommended by the NCEP include statins, bile acid resins, nicotinic acid, and ezetimibe. As in previous NCEP guidelines, the role of lifestyle modification is stressed. The full guideline can be viewed in the July 13th issue of *Circulation*, and highlights can be reviewed on-line at www.nhlbi.nih.gov.

Hypothyroidism and Pregnancy

A new study clarifies thyroid replacement therapy during pregnancy. Researchers at Harvard followed 19 women with hypothyroidism through 20 pregnancies, of which 17 resulted in full-term births. Thyroid function, HCG levels, and estradiol were measured before conception, every 2 weeks for the first trimester, and monthly thereafter. Oral doses of levothyroxine were increased during pregnancy to maintain preconception levels. The mean levothyroxine requirements increased 47% during the first half of pregnancy, plateaued by week 16, and remained

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

stable until delivery. The authors recommend that hypothyroid women, who become pregnant, should increase their levothyroxine dose by 30% as soon as pregnancy is confirmed, and should be monitored carefully throughout the duration of their pregnancy (*N Engl J Med*. 2004;351:241-249). Although simple in its design, this is an important study because it is estimated that 1 to 2% of all pregnant women are hypothyroid and need replacement therapy. Hypothyroidism during pregnancy is associated with poor fetal outcomes including impaired cognitive development and increased mortality. Clinicians now have a clear guide to levothyroxine dosing changes during pregnancy.

Anti-Depressants and the Risk of Suicide

The risk of suicidal behavior is relatively high after starting anti-depressants, however, there is no statistical difference between anti-depressants used, according to a new study. Researchers reviewed data from the UK General Practice Research Database from 1993 to 1999, and compared nearly 160,000 users of 4 anti-depressant drugs, 2 SSRIs and 2 tricyclics; fluoxetine, paroxetine, amitriptyline, and dothiepin (a trycyclic anti-depressant not marketed this country). The outcome was first-time non-fatal suicidal behavior, or suicide in treated patients vs comparable patients who did not exhibit suicidal behavior. The relative risks for non-fatal suicidal behavior were 0.83 for amitriptyline (95% CI, 0.61-1.13), 1.16 for fluoxetine (95% CI, 0.90-1.50), and 1.29 for paroxetine (95% CI, 0.97-1.70), compared to those using dothiepin. Perhaps the most startling finding in this study was the 4.07 relative risk for suicidal behavior within 9 days of starting any anti-depressant (95% CI, 2.89-5.74), compared to patients prescribed an anti-depressant 90 days or more before their suicidal behavior. Even more concerning, was a relative risk for fatal suicide among new users of anti-depressants of 38.0 (95% CI, 6.2-231). The authors found no significant associations between use of the various anti-depressants and the risk of suicide (*JAMA.* 2004;292:338-343, ed 379-380). The accompanying editorial points out the timeliness of the study, with regard to current congressional hearings in the use of anti-depressants in young adults. The authors point out that the data on patients aged 10 through 19 is limited however, and further study may be needed in this group.

FDA Actions

The FDA has approved acamprosate (Campral-Merck) for the maintenance of abstinence in patients in alcohol recovery programs. The drug, which has been available in Europe for several years, may not work if patients are still drinking or abusing other drugs when initiating therapy. Acamprosate's mechanism of action is unknown, but it appears to act in the central nervous system. Common side effects include diarrhea, nausea, vomiting, and abdominal pain.

The FDA has approved Merck and Schering-Plough's Vytorin for the treatment of hypercholesterolemia. The drug combines Merck's simvastatin (Zocor) with the jointly developed ezetimibe (Zetia), and is touted to be as potent as the so-called "super statins" atorvastatin (Lipitor) and rosuvastatin (Crestor). The new drug, which is expected to garner a hefty market share, will be priced at $2.30 a pill and should be available this fall.

Imiquimod (Aldera-3M) has received the expanded indication for treatment of superficial basal cell carcinoma. The drug, which is a topical immune modulator, was recently approved for treatment of actinic keratosis, and was initially approved for the treatment of venereal warts.

Brief Notes

The over-the-counter cough medications, dextromethorphan and diphenhydramine, are no better than placebo in suppressing cough in children (*Pediatrics.* 2004;114:e85-e90).

Many women are turning to phytoestrogens in lieu of hormone replacement therapy. The most commonly used of these, isoflavone soy protein, does not improve cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women (*JAMA.* 2004;292:65-74).

Ginseng reduces the effectiveness of warfarin in healthy volunteers. Patients on warfarin should be questioned as to their herbal supplement use (*Ann Intern Med.* 2004;141:23-27).