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INSIDE

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Dieting for Dollars

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: *Overweight employees who are paid to lose weight will do so in proportion to how much and how soon they are paid.*

Source: Finkelstein EA, et al. *JOEM.* 2007;49:981-989.

THIS WAS A PROSPECTIVE, RANDOMIZED STUDY OF 3 MATCHED groups of overweight workers who were recruited from North Carolina colleges by email, letters, and flyers. Internet access was required to participate in order to fill out surveys and undergo initial screening. Overall, the 201 participants had a mean BMI of 33 kg/m2, 89% were white, a majority were between 35 and 54 years old, and 76% were women. The participants were divided into three groups for the first 3 months: those who were encouraged to lose weight and received no immediate financial incentive, but were paid $14 for each percentage point of weight lost at 6 months; those who received $14 for each percentage point of weight lost from baseline to three months but no further incentive at 6 months, and those who received $7 for each percentage point of weight loss from baseline at baseline and another $7 for each further percentage point of weight lost at 6 months. Thus, at the end of the 6 month study period, payments were essentially equalized, so that all participants were able to earn $14 for each percentage of weight loss from baseline at either 3 or 6 months. For example, even if a person were in the group that received no payment for weight lost at 3 months, he/she could be paid $14 per percentage point weight loss at 6 months. In addition, everyone received $5 for attending the 3 month and the 6 month weigh-ins.

At the first weigh-in (3 months) those who were paid the most in the shortest time frame ($14 per percentage lost in the first 3 months) lost the most weight: an average of 4.7 pounds. They were also more likely to attend the weigh-in, and to have lost 5% of their initial weight at 3 months. Those who were paid $7 per percentage point lost an average of 3 pounds and those who were not scheduled to get paid until 6 months had only lost 2 pounds at three months. At 6 months, the biggest differences were in attrition from the study! A third of those

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who were paid $7 at each weigh-in had dropped out, compared with about half of those in either the deferred payment (54%) or early payment (45%) groups. Thus, analysis of the final results was hampered by the fact that only slightly more than half the participants still remained in the study. At 6 months (largely because of attrition) average weight loss between groups and the likelihood of achieving a 5% weight loss were not statistically different between groups, using an intention-to-treat approach. Try as I might, I was unable to tell from this paper if the group that was paid earliest was able to maintain the weight loss. However, those who were heavier to begin with lost the most weight, and those in the North Carolina University system lost more weight than those in the North Carolina Community College system. Non-whites were more likely to attend both weigh-ins than whites were, and the authors speculated that the modest financial incentives offered in this study might have represented a larger relative financial inducement to those with lower incomes. In their discussion, they note that the average payout at 3 months to those who were paid the highest amount at the shortest time period was $35 per subject. The authors concluded that "modest financial incentives can be effective in motivating overweight employees to lose weight."

COMMENTARY

Like many other medical articles about weight loss, this one received some play in the lay press ("Dollars help workers shed pounds."[1]) Given our persistent obesity epidemic despite intense study and efforts to address it, consideration of innovative approaches to weight loss seems reasonable. Several investigators have already explored linking financial rewards to weight loss in the context of weight loss programs,[1-4] but they have generally evaluated the effect of losing a financial deposit, rather than gaining "new" money for weight loss. The current paper breaks new ground, because it addresses the impact of the timing and amount of payment on weight loss in a worksite as a stand-alone (not as part of a weight loss program) intervention. It reminds me of the joke whose punch line is: "We have already established that. NOW we are just haggling." Some people will lose weight if paid to do so, and the current study suggests that the more money and the more quickly they are paid, the more likely they are to do so (duh). There are many remaining questions, not the least of which is whether workers can maintain weight loss in such a program, and whether it is ethical to reward people for getting unhealthy in the first place.

One of the most important questions is how to apply these findings to our daily clinical practice. Obese patients might benefit from rewards for weight loss. At the very least, we can notice this and compliment them. We can encourage their partners and significant others to reward them. And maybe they can set up internal inducements for themselves. ■

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Close Relationships and the Incidence of Coronary Events: Where is the Data?

ABSTRACT & COMMENTARY

By Joseph Varon, MD, FACP, FCCP, FCCM

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

Synopsis: *Coronary events occurred more commonly in patients who had experienced negative aspects of close relationships.*

Source: De Vogli R, et al. *Arch Intern Med.* 2007; 167:1951-1957.

THIS PROSPECTIVE, COHORT STUDY WAS CONDUCTED among nonindustrial civil servants aged 35 to

55 years who worked in London from 1985-1988. The phase I of this study included 9011 respondents of whom 6114 were men and 2897 were women. The participants were followed up for a period of 12.2 years. The association of negative aspects of close relationships as well as the incidence of new coronary artery disease (CAD) events was analyzed at the conclusion of the study. Specifically, in phase II of the study (1989-1990), participants answered a survey that included 15 items about negative aspects of personal relationships. Sources of negative aspects of personal relationships were divided into: partner or non-partner.

The main outcome variable analyzed was the incidence of new coronary events between phase II (1989-1990) and the end of the study (2003-2004). Coronary events included fatal and non-fatal acute myocardial infarction or angina.

Over the study period, negative close relationships were more likely to be experienced by younger individuals, women and men in the lower employment grades. There were 8499 participants that were free of CAD at enrollment, of whom 589 reported a coronary event during the study period. After adjustments for other variables, such as age, sex, marital status, obesity, diabetes mellitus, hyperlipidemia, and hypertension, a direct relationship was found between a stressful close relationship and new coronary events. Indeed, those participants that experienced high levels of negative close relationships were 1.34 times (95% Confidence Intervals 1.02-1.55) more likely to have a coronary event.

COMMENTARY

CAD remains a prevalent illness among Western societies. It is a serious disorder resulting in significant impairment of health or death. Clinicians tend to emphasize risk factors to avoid among their patients trying to prevent CAD. Among them, early diagnosis and treatment of hypertension, hyperlipidemia and diabetes mellitus are commonly sought and aggressively treated. The impact of stressful relationships, however, is often neglected

This study is particularly interesting because it corroborates prior research that has shown that the negative aspects of marital quality adversely affect the individual's health.[1] In the study by De Vogli and associates, the effect of negative close relationships was independent of any sociodemographic characteristic, pre-existing conditions and co-morbidities, psychosocial factors or health-related behaviors (ie, regular exercise, smoking, etc).[2] These negative close relationships were powerful predictors of health.

Even though the study was well designed from a statistical standpoint, readers must be aware that there may be a series of pathways that may link this association. For example, marital distress has previously been found to be associated with lack of exercise, alcohol intake, medical non-compliance.[3] High levels of anger have been found by other investigators and have been associated with CAD.[4] The specific biochemical role of negative relationships will likely require further research.

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How Low To Go for Hypertension in the Elderly

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California

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

Synopsis: *Diastolic blood pressures as low as 55mm Hg in the elderly were not found to be harmful when treating systolic hypertension; however, for those with known coronary heart disease, a minimum value of 70mm Hg is advised.*

Source: Fagard RH, et. al. *Arch Intern Med*. 2007;167(17):1884-1891.

Data from the Systolic Hypertension in Europe (Syst-Eur) Trial, a randomized, prospective placebo-controlled trial involving patients over age 59 in 198 centers, looked at 4,695 patients with systolic pressures between 160-219mm Hg and diastolic pressures under 95mm. Initial treatment consisted of a calcium channel blocker, with the addition of ACE-inhibitor and hydrochlorothiazide if needed. After an average period of 2 years, the control group was switched to active treatment along with the other treated group. Extended follow-up continued for 4 additional years. No increased cardiovascular mortality was observed with active hypertensive treatment that caused a diastolic pressure as low as 55mm Hg, if patients with baseline evidence of coronary heart disease were excluded.

The placebo group which had lower diastolic blood pressures without treatment had a higher incidence of cerebrovascular events, but not cardiac events. The treated group with low diastolic pressures had no increased risk for cerebrovascular events. Increased mortality from cancer and noncardiovascular causes was associated with low diastolic pressures in both the treated and placebo groups.

COMMENTARY

This study helps us determine how aggressively to treat systolic hypertension in the geriatric population. While we know that lowering systolic pressures is strongly recommended to prevent strokes and other cardiac events, this treatment may also result in a low diastolic pressure, which at a certain point becomes associated with a higher incidence of cardiovascular deaths (called the "J-curve"). Specifically, the Systolic Hypertension in the Elderly Program (SHEP) found that lowering the diastolic pressure to less than 70mm Hg caused more harm than benefit.[1] That study used treatment with chlorthalidone, and addition of beta-blockers and reserpine if needed.

However, this new analysis of the Syst-Eur Trial was able to separate out a subset of elderly patients with known coronary heart disease who had more risk with a lower diastolic pressure; for others, there was no increased cardiovascular mortality for a value as low as 55mm Hg. Although the SHEP trial showed an increase in cardiovascular events starting at 70mm diastolic pressure, with a 2-fold increase at 55mm, this was not the case in this new study when the group had no known pre-existing disease. The authors note that all deaths in both the control and treated groups from non-cardiac causes increase at lower diastolic pressures, suggesting that the J-curve observations may actually be caused by ill health and not by the low diastolic pressure.

Thus the conclusion is reached that we should treat systolic hypertension more aggressively, even if it causes a diastolic pressure as low as 55mm Hg, unless the patient has a risk of death from either cardiac or other causes. However, since many of the elderly will fall in this high-risk category, the general standard will likely continue to be a minimum diastolic pressure of 70mm, with a smaller healthy group eligible to receive the benefits of more aggressive therapy, even if it causes a pressure as low as 55mm Hg. ■

Reference

1. Somes GW, et al. *Arch Intern Med.* 1999;159(17):2004-2009.

Statin Withdrawal May Lead to Adverse Outcomes in Acute Stroke

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

Associate Professor, Department of Neurology, Weill-Cornell Medical College, Attending Neurologist, NewYork-Presbyterian Hospital

Dr. Segal is on the speaker's bureau for Borhringer-Ingelheim.

Synopsis: *Withdrawal of statin therapy in acute ischemic stroke may lead to increases in death and disability.*

Sources: Colivicchi F, et al. *Neurology.* 2007;69:904-910.

Statin therapy has a well-recognized role in the primary and secondary prevention of stroke. Statins may also have a neuroprotective effect in the setting of acute stroke. This has been well documented in animal models and high dose acute statin therapy is currently under investigation in human subjects. Pretreatment with statins is also likely to have benefit. Discontinuation of statins in the acute setting may precipitate vascular dysfunction and exacerbate ischemic events including both stroke and myocardial infarction.

In a single center study in Spain, Blanco and colleagues studied 215 patients with acute ischemic stroke, 89 of whom were previously taking statin medications. These patients were randomly assigned to have statin therapy withheld for three days (statin withdrawal group) or to be treated with 20 mg atorvastatin either orally or via nasogastric tube (statin treated group). All patients were treated with statins starting on day 4, including the 126 remaining patients who had not previously been treated with statin therapy (reference group).

At 3 months, 60% of patients in the statin withdrawal group met the primary outcome variable of death or dependence compared with 39% in the statin treated group. The adjusted odds ratio favoring a poor outcome among statin withdrawal patients was 2.39, increasing to 4.66 (1.46 - 14.91) after adjustment for age and stroke severity. Early neurological deterioration, defined as an increase of ≥ 4 points on the NIHSS, was observed in 65% of statin withdrawal patients compared with 21% of statin treated patients. Infarct volume was also greater in the statin withdrawal group, with a mean increase of 37 mL compared with treated patients. In post-hoc analyses, statin withdrawal patients also fared more poorly than

patients in the reference group with regard to all endpoints-death and dependency, early neurological deterioration and infarct volume.

In a related study, Colivicchi and colleagues studied 631 patients with an ischemic stroke and followed them for one year to assess their adherence to statin therapy. Among 409 patients who received atorvastatin therapy, 163 discontinued this medication and among 222 patients who received simvastatin, 83 had stopped taking this at one year. Among the 631 patients, 116 (18%) died during one-year follow up. After adjusting for confounding variables, including stroke severity, discontinuation of statin was an independent predictor of mortality with a hazard ratio of 2.78. This effect was more pronounced with early discontinuation, leveling off in the 9-12 month interval. Discontinuation of anti-platelet therapy was also an independent predictor of death, though with a less profound effect (hazard ratio of 1.81).

Statin therapy was discontinued due to side effects (most commonly dyspepsia) in a minority of patients (29%) and was unexplained in the remaining 71%. Patients who discontinued statins were older and more commonly female. Statins were more likely to be continued among patients who were diabetic or who had a history of previous stroke.

COMMENTARY

As Blanco indicates, animal as well as human data strongly suggest that withdrawal of statin therapy in an acute stroke patient may impair vascular function and trigger a dangerous inflammatory and prothrombotic state. This raises a major red flag in our treatment of acutely hospitalized stroke patients. Patients on previous statin therapy who have the medication discontinued face a 4.7 fold increase in their risk of death or dependency due to their stroke. This effect is even more pronounced than among patients not previously receiving statin medications.

These data raise important practical implications regarding the "nuts and bolts" of emergency room and immediate hospital care for acute stroke patients. Patients with severe strokes, who cannot take oral medications due to dysphagia, must receive these via nasogastric tube. Such patients are commonly made NPO, with feeding and oral medication administration delayed until their swallow status can be clarified. These issues are particularly germane to patients receiving thrombolysis. Among patients receiving intravenous tPA, our protocol mandates placement of a Foley catheter prior to thrombolysis since such an invasive procedure cannot be performed once tPA has been administered. The same would likely apply to a nasogastric tube.

The data of Colivicchi are more difficult to understand. Discontinuation of statin therapy was highly associated with post-stroke mortality, but it is not clear if this was a cause, or more likely merely an effect of practice patterns among patients with more devastating strokes. It is testament to the inconclusive nature of this study that the justification for cessation of statin therapy was unexplained in over 70% of patients. In addition, while over 80% of the deaths were attributed to cardiovascular causes, data such as this, gleaned from death certificates, is unlikely to reflect the true etiology of their demise. Notably, recurrent stroke was not documented as the cause of death among any of the patients from whom statins were withdrawn. ■

Pharmacology Update

Raltegravir Tablets (Isentress™)

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.

The FDA has approved the second of two new antiretroviral agents from new drug classes. Raltegravir is the first integrase strand transfer inhibitor and follows closely on the approval of maraviroc, a CCR5 co-receptor antagonist. Integrase is an enzyme that is essential for HIV-1 replication by catalyzing the insertion of HIV DNA into the genome of the host cell. Raltegravir is marketed by Merck & Company as Isentress.

Indications

Raltegravir is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in treatment-experienced adults who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.[1]

Dosage

The recommended dose is 400 mg taken orally twice daily. It may be taken without regard to meals. Dosage adjustment is not needed for patients with renal impairment or mild to moderate hepatic impairment.[1]

Raltegravir is available as 400 mg tablets.

Potential Advantages

Raltegravir has a different target of antiretroviral action than existing drugs. It does not interact with substrates, inhibitors, or inducers of CYP 450 isoenyzmes and does not inhibit UDP-glucuronosyltransferases or P-

glycoprotein-mediated transport.[1]

Potential Disadvantages

The most common adverse events are diarrhea (17%), headache (10%), nausea (10%), and pyrexia (5%). Elevation of creatine kinase has been reported with frequencies of grade 2 to 4 elevations of about 2%. Myopathy and rhabdomyolysis have been reported.[1] Raltegravir is a substrate of uridine diphosphate glucuronosyltransferase (UGT1A1) and should not be used with strong inducers of this enzyme (eg, rifampin). It can be used with atazanavir, a strong inhibitor of UGT1A1.[1]

Comments

Raltegravir is the first integrase strand transfer inhibitor to be approved. Integrase is one of the three enzymes essential for viral replication. Raltegravir has shown in vitro activity against multidrug resistant and both CCR5 and CXCR4 tropic virus.[2] FDA approval was based on two ongoing, 24-week, randomized, phase III, double-blind, placebo-controlled studies (BENCHMRK 1 and BENCHMRK 2) in treatment-experienced adult subjects with documented resistance to at least one drug in each of the 3 classes (NRTI, NNRTI, PI) (n = 699).[1] Subjects were randomized to raltegravir (400 mg twice daily) and optimized background therapy (OBT) or placebo plus OBT stratified by degree of resistance and enfuvirtide use. Selection of OBT was by the investigator with consideration of genotypic/phenotypic results and prior antiretroviral therapy. The median baseline plasma HIV-1 RNA values were 4.8 log10 copies/ml and 4.7 log10 copies/ml for raltegravir and placebo. Median baseline CD4+ values were 119 cells/mm3 and 123 cells/mm3 respectively. At 24-weeks, mean changes in viral loads were -1.85 log10 copies/ml for raltegravir and -0.84 for placebo. Mean increases in CD4+ were 89 cells/mm3 and 35 cells/mm3 respectively. Approximately 2/3rd of subjects with data at 24-weeks (62%) achieved viral load < 50 copies/ml with raltegravir compared to 1/3rd for placebo. Thirteen percent of subjects showed a rebound in viral RNA (>400 copies/ml or > 1 log10 increase above nadir) after achieving a 1 log10 decline or <400 copies/ml. Raltegravir appears to be well tolerated.[1,3] In a small study involving treatment naïve subjects (n = 198), raltegravir was found to be as effective as efavirenz when combined with tenofovir and lamivudine.[4] It is currently not FDA approved for this use. Raltegravir is expected to cost about $9850 per year.

Clinical Implications

Raltegravir offers a drug that targets a different aspect of HIV-1 replication. The long-term safety and effectiveness is not known as approval was based on improvement in surrogate endpoints. ■

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4. Markowitz M, et al. J Acquir Immune Defic Syndr. 2007;46:125-133.

CME Questions

53. When employees are paid to lose weight:

a. most of them will continue to participate in the program, even if they don't lose weight.
b. those who are least overweight will lose the most weight.
c. the short-term benefits are greatest for those who are paid the most.
d. measurable effects on weight do not occur.

54. In the study by De Vogli and coworkers, coronary events:

a. were more likely to occur in patients with morbid obesity
b. occurred more commonly among high-salary employees
c. were 2.3 times more likely to occur among married men
d. occurred more often among those with high level of negative aspects of close relationships
e. were based on a pre-existing history of coronary artery disease

Answers: 53 (c); 54 (d)

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.

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.

Sexual Dysfunction in Women with Metabolic Syndrome: Nutrition Intervention

It has been demonstrated that women with metabolic syndrome (MBS) have a higher prevalence of sexual dysfunction. Indeed, each of the individual components of MBS has been independently associated with greater frequency of female sexual dysfunction (FSD)

Clinical trials of the Mediterranean Diet as a secondary prevention intervention for MI have shown startlingly good outcomes, reducing MI by as much as 70%. Some of the benefits of the Mediterranean diet are attributed to improved endothelial function. Whether dietary intervention in women with MBS might ameliorate sexual dysfunction was the subject of this investigation.

This study selected women with FSD and MBS. Exclusions included smokers, a prior history of CV disease, any regular medication, and alcohol abuse. The Female Sexual Function Index (FSFI), which measures desire, arousal, lubrication, orgasm, satisfaction, and pain, was the primary trial metric.

Fifty-nine women were assigned to either Mediterranean Diet or control. The intervention group received dietary counseling, including a meeting with a nutritionist monthly for the first year, and bimonthly for the second year.

At the end of the trial, scores on the FSFI increased from 19.7 to 26.1 in the treatment group, but did not change in the control group. Each of the subcategories in the FSFI were favorably impacted. For women with MBS, utilization of the Mediterranean Diet may improve sexual dysfunction. ■

Esposito K, et al. Int J Impotence Research. 2007;19:486-491.

Confirming the Diagnosis of Premature Ejaculation

According to large population surveys, premature ejaculation (PEJ) is the most common sexual dysfunction in America. The definition becomes problematic, however, because DSM-IV criteria lack concreteness: "ejaculation before the person wishes it," or "causing marked distress of interpersonal difficulty." These descriptors are generally appropriate, but open to a wide range of interpretation. Even the amount of time prior to ejaculation which might be used as a clinical benchmark has been much debated, but intravaginal ejaculatory latency of less than 1.0-1.5 minutes is generally accepted as PEJ.

The Premature Ejaculation Diagnostic Tool (PEDT) was developed to assist clinicians in diagnosis of PEJ. This trial compared the PEDT with DSM-IV and actual expert clinician diagnosis of PEJ. Men with complaints of PEJ (n=102) were screened with the PEDT and individually interviewed by a clinician expert in male sexual dysfunction.

The concordance of PEDT results with DSM-IV and expert clinician diagnosis was excellent. Although clinicians may appropriately rely on direct patient interviewing rather than formalized sexual function scales to diagnose sexual dysfunction, the PEDT provides a tool that is simple to administer and accurate. ■

Symonds T, et al. Int Jour Impotence Research. 2007;19:521-525.

A Possible Relationship Between CAD and Colonic CA

Colon cancer and Coronary Artery Disease rank at the top of causes of death worldwide. A 2006 retrospective study indicated a strong relationship between them, some of which might be explained by shared risk factors (eg, smoking, diabetes, sedentary lifestyle, obesity). A cross-sectional study of residents of Hong Kong who were being evaluated for coronary artery disease (n = 414) provided the subjects for this report. From the large group of persons selected to undergo screening for CAD, subjects were divided into those with and without CAD subsequent to evaluation. Then, subjects were compared with age/sex matched controls from the general population. Participants underwent colonoscopy within 8 weeks, or when stable if an acute coronary disorder was present.

The prevalence of any colonic neoplasm was almost twice as great (34.0% vs 18.8%) in persons with proven CAD vs no-CAD. Specifically addressing colon cancer, the prevalence amongst the subgroup identified with CAD was almost ten-fold greater than CAD screenees without CAD (4.4% vs 0.5%).

As has been identified in other settings, smoking and the metabolic syndrome were associated with an increased risk of colonic neoplasia. The results of this study suggest that clinicians have a high level of vigilance for colonic neoplasia in persons who have been proven to have CAD. ■

Chan AOO, et al. JAMA. 2007;298(12):1412-1419.

A Cryptic Dialysis Tracing

By Ken Grauer, MD, Professor, Department of Community Health and Family Medicine, University of Florida
Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

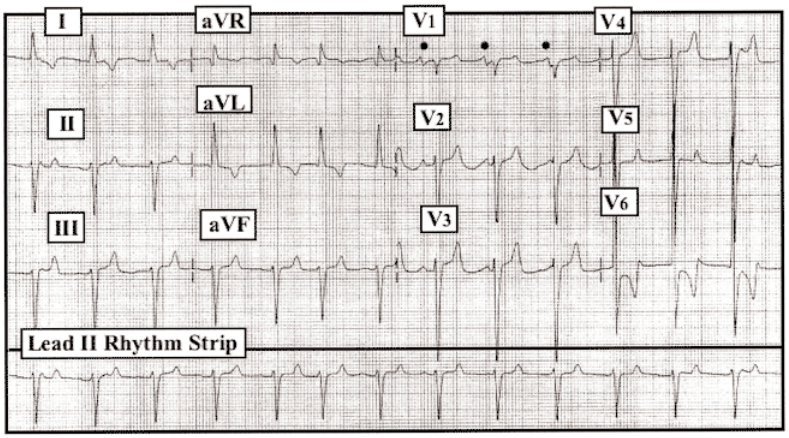

Figure: 12-lead ECG obtained from an 81-year-old man with bradycardia.

Clinical Scenario:

The 12-lead ECG and lead II rhythm strip seen in the Figure was obtained from an unfortunate middle-aged dialysis patient with a dilated cardiomyopathy. He had missed his last dialysis treatment. The patient was hypertensive, fluid overloaded and dyspneic with chest pain at the time this tracing was recorded. Given this clinical context, how would you interpret his ECG?

Interpretation/Answer:

It is difficult to be certain what the rhythm is in this tracing. P waves are not consistently seen and QRS complexes are not completely regular in this Lead II rhythm strip. Nevertheless, small amplitude upright P waves do appear to precede at least some QRS complexes. That atrial activity of some kind is present is clear from lead V1 (dots in this lead), although the changing PR interval in lead V1 suggests that there may be at least transient AV dissociation with an intermittent accelerated junctional rhythm that is punctuated by sinus or other supraventricular beats. A longer rhythm strip in a lead showing more clearly defined P wave morphology would be needed to know for sure.

The QRS complex appears to be slightly prolonged (we estimate 0.11 second in duration). That said, QRS morphology and the suggestion that at least some of the P waves are conducting strongly favor this to be a supraventricular rhythm. There is marked LAD (left axis deviation), consistent with LAHB (left anterior hemiblock). QRS amplitude in the precordial leads is greatly increased, consistent with LVH (left ventricular hypertrophy). Transition is difficult to identify due to overlap of high amplitude QRS complexes, but the R wave appears to become greater than the S wave between leads V5 and V6. Deep S waves persist across the precordium. The most remarkable finding on this tracing resides in assessment of ST-T wave morphology. T waves are tall and peaked with a relatively narrow base in several leads (leads III, aVF, and V2 through V4). This T wave shape persists in the form of a smaller T wave complex in transitional lead V5, before development of a peaked and deeply negative T wave in lead V6. T waves are also inverted in leads I and aVL. Overall QRST morphology is consistent with LVH and "strain" and/or ischemia, with T wave peaking in this dialysis patient suggesting possible hyperkalemia. Serum potassium turned out to be significantly elevated. Clinical points to keep in mind are that it will be difficult to assess ST-T wave morphology for acute ischemia or infarction in the presence of hyperkalemia (ie, "competing conditions", in which ST depression and T wave inversion may at least in part be counteracted by hyperkalemic T wave peaking). Finally, some patients with hyperkalemia manifest deeply negative T wave peaking, as is evident here in lead V6. ■

In Future Issues:

Does Tai Chi Prevent Falls in Elderly?

PHARMACOLOGY WATCH

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.

Are Thiazolidinediones (TZDs) Safe?

In this issue: *Are thiazolidinediones safe? New study shows Zometa reduces risk of hip fractures and improves survival; Merck HIV vaccine proven ineffective in clinical trials; no causal association found between exposure to mercury from thimerosal; and FDA approvals.*

There's no hotter topic in medicine right now than the safety of the thiazolidinediones (TZDs) rosiglitazone (Avandia) and pioglitazone (Actos). Several meta-analysis have pooled data from multiple clinical trials and come to different conclusions regarding the safety of the drugs. The September 12 issue of *JAMA* contained two papers, both meta-analysis, the of first which suggests that pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. An increase in heart failure was noted, although no increase in mortality (*JAMA* 2007; 298:1180-1188).

The second paper looked at rosiglitazone and noted that in patients with impaired glucose tolerance or type 2 diabetes, use of rosiglitazone for at least 12 months was associated with a significantly increased risk of myocardial infarction and heart failure, again without a significant increase risk of cardiovascular mortality (*JAMA* 2007; 298:1189-1195). This followed on conflicting meta-analysis regarding the risk of rosiglitazone published in the *New England Journal of Medicine* in June and July, the first of which suggested the rosiglitazone was associated with an increase risk of myocardial infarction and increased risk of death from cardiovascular causes (*NEJM* 2007; 356:2457-2471), while the second showed an increased risk of heart failure but no increased risk of myocardial infarction or death from cardiovascular causes (*NEJM* 2007;357:28-38). The studies led to congressional hearings, multiple editorials in medical journals and eventually led the FDA to recommend black box warnings regarding the risk of heart failure for both drugs in July. But despite cries from consumer groups suggesting that this was the Cox-2 debacle redux, the FDA stopped short of taking rosiglitazone off the market. The most recent entry into the fray is a new meta-analysis from the Lahey Clinic in Boston. This review analyzed over 3000 studies of which 7 were used for the analysis—all randomized double-blind clinical trials of drug-related congestive heart failure in prediabetic or diabetic patients given either rosiglitazone or pioglitazone. In over 20,000 patients, 360 had congestive heart failure, 214 on TZDs and 146 on comparators. As with other studies there was an increase risk of heart failure associated with both drugs (relative risk 1.72, 95% CI 1.21-2.24, P= 0.002), but again no increase in cardiovascular death was noted with either drug (RR 0.93). The authors suggest that TZDs cause worsening heart failure, but are not associated with progressive systolic or diastolic dysfunction of the left ventricle that leads to death. They also suggest that more studies are needed (*Lancet* 2007;370:1129-1136). The take home message from all the studies is to use caution in TZDs in patients with diabetes and heart failure (NYHA I and II), and to carefully monitor patients for worsening signs and symptoms including weight gain and edema. Initiation of these drugs in patients with established NYHA Class III or IV heart failure is contraindicated.

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Zometa and hip fractures

A single 5 mg infusion of zoledronic acid (Zometa) within 90 days of a hip fracture reduced the risk of new fractures and improved survival according to new study. Zoledronic acid is a long acting bisphosphonate that is approved for once yearly treatment of postmenopausal osteoporosis. The drug is effective at reducing vertebral, hip, and non-vertebral fractures in women with osteoporosis. In this current study, 1065 men and women with hip fractures were assigned to receive yearly intravenous zoledronic acid 5 mg IV or placebo, the infusions were administered within 90 days of surgical repair of a hip fracture. All patients received vitamin D and calcium. Mean age was 74.5 years, with approximately 75% women. The rate of new clinical fracture was 8.6% in the zoledronic acid group and 13.9% in the placebo group (35% risk reduction, $P = 0.001$). The respective rates of new clinical vertebral fractures were 1.7% vs 3.8% ($P = 0.02$) and for non-vertebral fractures 7.6% vs 10.7% ($P = 0.03$). The death rate was 28% less in the zoledronic acid group (101 of 1054 [9.6%] vs 141 of 1057 [13.3%], $P= 0.01$). No cases of osteonecrosis of the jaw were reported and no adverse effects of healing fractures were noted. The authors conclude that an annual infusion of zoledronic acid within 90 days of a low trauma hip fracture was associated with reduced rate of new fractures and improved survival (published early at www.NEJM.org September 17, 2007).

Merck HIV Vaccine Ineffective in Clinical Trial

After years of development and clinical trials Merck has announced that their HIV vaccine is ineffective in a large clinical trial, and the company has halted further test vaccinations. Other HIV vaccines have also failed but many had hoped that the Merck vaccine, which worked by stimulating T cells, might be more effective. The trial, which was begun in 2004 vaccinated 3000 uninfected volunteers in the US and Latin America. Among 741 patients who received a least one dose of the vaccine, 24 new HIV infections were identified, compared to 21 infections in 762 patients who received placebo. Work continues on other HIV vaccines, currently 30 worldwide are in clinical trials, but the failure of the Merck vaccine is seen is a major setback for HIV researchers.

Thimerosal and Mercury Exposure

Thimerosal has been the subject of intense scrutiny for years regarding its potential link to various neuropsychological deficits in children. Thimerosal has been used as a preservative in vaccines and gamma globulin for decades, although it is rarely used now because it is metabolized to mercury and thiosalicylate, potentially leading to high mercury levels in children. In a new study from the CDC and several large HMOs, 1047 children between ages of seven and 10 years were enrolled and tested for 42 neuropsychological outcomes, then the medical records were examined for history of exposure to mercury from thimerosal. Prenatal mercury exposure from thimerosal was associated with better performance on one measure of language and poor performance on one measure of attention and executive functioning. Exposure in infancy up to seven months old was associated with better performance in one measure, fine motor coordination, and on one measure of attention and executive functioning. Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination. The authors conclude that they could not find a causal association between early exposure to mercury from thimerosal and deficits in neuropsychological functioning at age 7 to 10 years (*NEJM* 2007; 357: 1281-1292).

FDA Actions

Eli Lilly has received approval from the FDA to market raloxifene (Evista) for the indication of reducing the risk of breast cancer in postmenopausal women with osteoporosis and postmenopausal women who are at high risk for invasive breast cancer. Raloxifene is a selective estrogen receptor modulator (SERM) that is already approved for prevention and treatment of osteoporosis in postmenopausal women. The drug was recently required to add labeling regarding an increased risk of fatal strokes in women taking the drug. It also carries a black box warning regarding risk of thromboembolism in women who are at high risk (those with an active or past history or thromboembolism).

Just in time for the winter flu season, the FDA has approved nasal influenza vaccine (FluMist) for use in children between the ages of 2 and 5. Previously the vaccine was only approved for children 5 years old and older and adults up to age 49. The CDC is recommending all children between the ages of 6 months to 59 months receive a flu vaccine. Children ages 2-8 who have never received a flu vaccine will initially require two doses of fluMist at least one month apart.

The FDA has approved a new oral granules form of terbinafine for the treatment of tinea capitis (ringworm) in children. The preparation may be sprinkled on food, allowing easier administration to children who may not otherwise take medicine over the two weeks required to treat tinea. Terbinafine granules are indicated for the treatment of tinea capitis in children age 4 years and older. It is marketed by Novartis AG as Lamisil Oral Granules. ■