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The Hope Trial

ABSTRACT & COMMENTARY

Synopsis: *ACE inhibition with ramipril caused a significant reduction in cardiovascular end points as well as a decrease in the development of diabetes and renal dysfunction.*

Source: American Heart Association Annual Scientific Sessions, November 7-10, 1999, Atlanta, GA.

The heart outcomes prevention evaluation (hope) trial randomized 9541 high-risk patients to the angiotensin-converting enzyme (ACE) inhibitor ramipril (10 mg/d) or placebo and vitamin E (400 IU/d) or placebo for a mean follow-up period of 4.5 years. This international study was carried out in 267 hospitals and 19 countries, with the majority of patients coming from the United States. The ramipril arm was stopped in early 1999 because of a favorable outcome for the ACE inhibitor; the vitamin E arm has continued. The study population consisted of individuals with documented coronary artery disease (CAD), cerebrovascular, or peripheral vascular disease. In addition, diabetics without vascular disease with at least one additional CAD risk factor were enrolled. All individuals were older than 55 years of age. Patients had no history of heart failure; hypertensives could be enrolled if blood pressure was controlled (46% had hypertension). Thirty-eight percent had diabetes, 11% had a previous stroke, 43% had peripheral vascular disease, and two-thirds had an elevated cholesterol level. Eighty-one percent of all patients had CAD, half with a prior myocardial infarction (MI). The results were striking, with a robust 20-25% reduction in relative risk favoring ramipril for all vascular end points. (*See Table*.) There was a 22% reduction in the primary end point of cardiac death, stroke, or nonfatal MI (17.7% vs 14.1%). There was a major decrease in stroke and in new heart failure as well as for revascularization. Of interest, new onset diabetes was decreased by 32% (P = 0.002). New renal dysfunction/dialysis or microalbuminuria was also decreased by ramipril. An echo substudy of approximately half the entire cohort (mean ejection fraction of 60%) demonstrated comparable risk reductions for all end points as the entire cohort. Higher risk patients had a greater reduction in events than those at lower risk. It was concluded that lowering of blood pressure only accounted for a small proportion of the

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INSIDE

decrease of MI and other end points; individuals in the highest quartile of baseline systolic blood pressure had the greatest risk reduction. The hypertensive and nonhypertensive patients had no difference in benefit from ramipril. Vitamin E had no effect on total mortality, cardiovascular deaths, or other end points.

■ COMMENT BY JONATHAN ABRAMS, MD

These data have already achieved considerable attention and were formally announced at the European Cardiac Society Meeting at the end of August. The benefits of the ACE inhibitor in individuals who ordinarily would not be treated with such a drug are impressive and concordant with a large amount of vascular biology research, endothelial function studies, and mechanistic hypotheses regarding prevention or slowing progression of vascular disease. These data raise the question as to whether *all* individuals who meet the HOPE criteria should be treated with an ACE inhibitor. Given that the entire cohort had an event rate of cardiac death, stroke, or MI of greater than 3% per year, it seems reasonable that for patients with documented vascular disease, representing the majority of the HOPE cohort, or individuals at high risk for future events (e.g., diabetics with risk factors or those with multiple CAD risk factors), ACE inhibitor therapy should be considered. There is considerable disappointment regarding the antioxidant hypothesis because of the null effects of vitamin E. Earlier data this year from the GISSI-3 trial were also negative in a large population given vitamin E. Some believe that the combination of vitamin E and vitamin C, or the use of different antioxidants, will be necessary to really test the oxidation hypothesis. Certainly, HOPE and GISSI-3 deflate the present enthusiasm for routine use of antioxidant vitamins. (*Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.*) ❖

Table

HOPE	End Points (Ramipril vs Placebo)			
	RAM (%)	PLAC (%)	P Value	RR
CV death, MI, or stroke	14.1	17.7	0.001	0.78
All MI	9.8	12.0	0.0005	0.80
CV death	6.0	8.0	0.0002	0.75
NMFI	5.9	7.5	0.0002	0.78
Revascularization	16.0	18.6	0.001	0.85
All death	10.3	12.2	0.003	0.83
Stroke	3.4	4.9	0.0002	0.68
Nondiabetes	3.7	5.3	0.002	0.68
CHF	9.2	11.7	0.002	0.77

Note: The *New England Journal of Medicine* has taken the unusual step of premature electronic publication of this trial on its electronic website: (http://www.nejm.org/content/yusuf/1.asp).

Antimicrobial Residues in Food: What is too Much?

INFECTIOUS DISEASE UPDATE

Synopsis: *Given the public health effect of increasing bacterial resistance, the FDA is re-examining this policy as it reviews newer data on the effect of antimicrobial residues in food on intestinal flora.*

Source: Auit A. *Lancet* 1999;354:1190.

The increasing presence of vre and other multidrug-resistant organisms in human intestinal flora is

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an increasing public health hazard. Evidence suggests that these organisms are being introduced into the human population from a number of different sources, including animal feed and possibly in the food we eat, and also as the result of frequent exposure to antimicrobials. Following prompting by a Joint Committee of the WHO and the Food and Agriculture Organization of the United Nations, which recommend acceptable daily intake and maximum residue limits of antimicrobials from meat and other dietary products, the FDA in 1996 established a policy limiting the daily exposure of Americans to no more than 1.5 mg of antimicrobial residues in food. This policy was more liberal than that of our European and Japanese counterparts.

COMMENT BY CAROL A. KEMPER, MD

Given the public health effect of increasing bacterial resistance, the FDA is re-examining this policy as it reviews newer data on the effect of antimicrobial residues in food on intestinal flora. (*Dr. Kemper is Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center.*) ❖

Stroke Prevention in Patients with Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *Antithrombotic agents reduce the risk of stroke in nonvalvular atrial fibrillation.*

Source: Hart RG, et al. *Ann Intern Med* 1999;131: 492-501.

In this paper, hart and associates performed a meta-analysis of data from 16 randomized clinical trials of antithrombotic therapy for patients with nonvalvular atrial fibrillation. The 16 trials included a total of 9874 participants, including 2239 patients who were assigned to placebo.

Six trials involving 2900 patients compared adjusted-dose warfarin with placebo or control. The mean age of participants at study entry was 69 years, with 29% of the patients being women. The control stroke rate was 4.6% and 12.3% per year for primary and secondary prevention trials, respectively. Meta-analysis showed that therapy with adjusted-dose warfarin reduced the relative risk of stroke by 62%. The absolute risk reduction for all strokes was 2.7% per year in primary prevention and 8.4% per year in secondary prevention. All-cause mortality was decreased by 26% in patients who received warfarin.

Six trials compared antiplatelet therapy vs. placebo. Approximately 90% of total follow-up exposure during antiplatelet therapy was with aspirin alone. The aspirin dosage ranged from 25 mg twice daily to 1300 mg daily. The mean age of participants was 70 years, with 38% women. The average rate of stroke among participants assigned to placebo was 5.2% per year for primary prevention and 12.9% per year for secondary prevention.

Meta-analysis of all six trials showed that aspirin reduced the incidence of stroke by 22%. The absolute risk reduction was 1.5% per year for primary prevention and 2.5% per year for secondary prevention.

Adjusted-dose warfarin was compared to aspirin in five trials involving 2837 patients. The mean age of participants was 71 years and 38% were women. The results of these comparisons were variable but meta-analysis showed that adjusted-dose warfarin reduced overall relative risk for stroke by 36%. The paper also lists data from trials that compared adjusted-dose warfarin with fixed doses of warfarin and aspirin and a number of other antithrombotic regimens. However, these trials were sufficiently different to prevent meaningful use of meta-analysis to combine results. Hart et al then present a table giving the estimated size of treatment effects according to risk status. The greatest benefit is seen with warfarin compared to aspirin in high-risk patient groups, with a 48% reduction with warfarin seen for secondary prevention and a 24% reduction for primary prevention in these subgroups.

Hart et al conclude that there is conclusive evidence from a large number of randomized trials that antithrombotic agents reduce the risk of stroke in nonvalvular atrial fibrillation.

COMMENT BY JOHN P. DiMARCO, MD, PhD

This paper summarizes two decades of clinical trials in the field of stroke prevention among patients with atrial fibrillation. By combining data from these trials in a meta-analysis, Hart et al give physicians a better estimate of the magnitude of treatment effect of such therapy.

The most valuable parts of this meta-analysis are the comparisons of warfarin vs. placebo, aspirin vs. placebo, and warfarin vs. aspirin. It is clear that warfarin is superior to aspirin or aspirin plus low, fixed-dose adjusted warfarin in high-risk populations. Here, the magnitude of treatment effect is substantial and the risk of excess bleeding relatively modest. Controversy about the role of warfarin still exists, however, for relatively low-risk patients. Here, there is only a modest benefit achieved with warfarin over aspirin or even over placebo, but the excess risk of hemorrhage is still present. A possible con-

clusion from these data is that physicians should still exercise judgment when considering warfarin for patients at low risk for stroke. A conservative approach may be appropriate for patients at low risk but physicians should be aggressive in the use of warfarin in patients at high risk. High-risk factors include: older women, patients with prior stroke or transient ischemic attack (TIA), and those with hypertension and diabetes.

Table

ACCP Recommendations

Age	High Risk	Antithrombic
< 65 yrs.	No	Aspirin
	Yes	Warfarin
65-75 yrs.	No	Aspirin or Warfarin
	Yes	Warfarin
> 75 yrs.	All	Warfarin

It is disappointing that this meta-analysis does not allow us to show any regimen superior to adjusted-dose warfarin. Although a large number of alternative antithrombotic strategies have been tested, none has proved to be superior to warfarin. Anticoagulation with warfarin is still difficult and one hopes that in the future some effective alternative strategy may be identified. Until then, the recommendations of the American College of Chest Physicians (*Chest* 1998) (*see Table*) are worth considering. (*Dr. DiMarco is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.*) ❖

Partial ACL Tears

ABSTRACT & COMMENTARY

Synopsis: *Partial ACL ruptures involving less than 50% of the ligament have a good prognosis over the long term.*

Source: Messner K, Maletius W. *Am J Sports Med* 1999; 27:455-459.

Partial anterior cruciate ligament (acl) tears occur less frequently than complete ruptures, and there is uncertainty surrounding their long-term significance. As one would expect, the amount of instability that develops appears proportional to the degree of initial injury. However, little is written concerning the natural history of partial ACL tears over the long term.

Messner and Maletius have followed a group of 22 consecutive patients with a partial ACL tear for a mean of 20 years (range, 18-25). All patients but one, who died, were available for evaluation, which is truly remarkable after such a long period. In each case the diagnosis of a partial ACL tear was made by arthroscopy and an examination under anesthesia within 10 days of injury. No patient had greater than 1+ anterior laxity or greater than 50% damage to the ligament.

Three patients had suture repair of the partially torn portion of the ACL, while all other partial ACL injuries were treated nonoperatively. Nine patients with greater than 2+ valgus laxity underwent primary repair of the medial collateral ligament (MCL), a procedure commonly performed 25 years ago. All patients had concomitant acute injuries in the knee. The period of initial immobilization of the knee depended on these concomitant injuries rather than the ACL and ranged from one to six weeks.

Patients were evaluated at 12 and again at 20 years post-injury by physical exam, instrumented arthrometry, weight-bearing X-rays, Tegner score for activity level, and Lysholm score for knee function. At the latest follow-up, quadricep strength was assessed and quality-of-life issues were measured by an SF-36 health survey.

During the entire follow-up period, no patient underwent ACL reconstruction. Two patients had arthroscopy for meniscal tears and one patient had a late MCL injury. At the latest follow-up, 17 of 21 patients had Lysholm scores in the excellent range, and quality-of-life scores were generally better than those of a reference sample in the general population. Although only 13 of 22 patients were able to initially return to their preinjury activity level, the Tegner scores did not deteriorate between the 12- and 20-year time points.

At 20 years, 10 knees had a 1+ Lachman exam, two knees a 2+ Lachman, and one knee a positive pivot shift. Instrumented laxity measurements were less than 3 mm, which is considered normal, for 20 of 21 knees. About half the knees developed mild arthritis by X-ray, with little progression between 12 and 20 years. Four patients had more advanced changes.

COMMENT BY DAVID R. DIDUCH, MS, MD

From this excellent longitudinal prospective study by Messner and Maletius, we can conclude that partial ACL ruptures involving less than 50% of the ligament have a good prognosis over the long term. No patient underwent late ACL reconstruction over a 20-year follow-up period. However, because these were major knee injuries with concomitant damage to other structures in every case, few patients returned to the same level of preinjury sports activities. Given that the vast majority of patients developed only mild ACL laxity by exam or

arthrometry, we might conclude that these other injuries were more significant over the long run.

Therefore, we can advise our patients with partial ACL injuries involving less than 50% of the ligament to not develop progressive laxity and to remain reasonably active. The difficulty clinically can be in determining whether the ACL is only partially torn with less than 50% ligament involvement. Magnetic resonance imaging (MRI) can be helpful in this regard and can be confirmed by instrumented laxity measurements. Arthroscopy, together with an exam under anesthesia, can be added when the diagnosis and treatment are in doubt. Some objective information is encouraged because patient guarding during the physical exam can confuse the picture and underestimate the degree of laxity. Of course, even partial tears by MRI that demonstrate clinical laxity by history and exam are functionally complete tears and should be treated as such.

Thus, this paper, despite the small number of patients, is an important addition to the ACL literature given the extremely long follow-up in nearly all patients. True partial ACL tears do well over the long term. The major limiting factor appears to be associated injuries. Just as with complete ACL tears, preserving the meniscus appeared to have the greatest influence on late arthritic changes. These findings will be helpful in the future as we counsel patients regarding optional treatment. (*Dr. Diduch is Assistant Professor, Department of Orthopaedic Surgery, University of Virginia School of Medicine, Charlottesville, VA.*) ❖

Pharmacology Update

Pioglitazone Tablets (Actos)

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

The fda has approved a new thiazolidinedione for the treatment of type 2 diabetes mellitus. Eli Lilly and Takeda's pioglitazone (Actos) is the third drug in this class, joining troglitazone (Rezulin) and the recently approved rosiglitazone (Avandia). Thiazolidinediones improve insulin sensitivity by acting as potent agonists for the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) that regulate the transcription of insulin-responsive genes.[1] Sites of action include the liver, adipose tissue, and muscle tissue resulting in a decrease in fasting plasma glucose and insulin.

Indications

Pioglitazone is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. The drug can be used as monotherapy or in combination with sulfonylurea, metformin, or insulin when diet and exercise plus the single agent is inadequate in achieving glycemic control.[1]

Dosage

The recommended initial dose for monotherapy is 15 mg or 30 mg once daily. The dose may be increased in increments up to 45 mg once daily. When used in combination with a sulfonylurea, the initial dose is 15 mg or 30 mg once daily. The dose of the sulfonylurea should be reduced if the patient experiences hypoglycemia. A similar initial dose is recommended for use in combination with metformin or insulin. In patients receiving insulin and pioglitazone, the insulin dose can be reduced by 10-25%.[1] The drug may be taken without regard to meals.

Baseline alanine transaminase (ALT) should be determined before initiating therapy and therapy should not be initiated in patients with baseline ALT more than 2.5 × ULN. Therapy should be discontinued if ALT exceeds 3 × ULN or if the patient is jaundiced.

Pioglitazone is supplied as 15 mg, 30 mg, and 45 mg tablets.

Potential Advantages

In clinical trials involving more than 4500 subjects, no evidence of drug-induced hepatotoxicity or elevation of ALT levels has been reported.[1] The incidence of ALT values equal to or greater than 3 × ULN was 0.26% and 0.25% for pioglitazone and placebo, respectively.[1] Due to the chemical similarity between pioglitazone and troglitazone, the FDA is still recommending that serum ALT be evaluated prior to initiation of therapy and every two months for the first year, and periodically thereafter.[1] Pioglitazone has been reported to produce a modest reduction in triglyceride levels (50 mg/dL and increase in HDL cholesterol (7-8 mg/dL).[8]

Potential Disadvantages

Edema has been reported in 4.8% of pioglitazone-treated patients compared to 1.2% for placebo-treated patients. Edema was more frequently reported in patients on pioglitazone/insulin combinations. Mean hemoglobin values have declined by 2-4%, which generally occurred within the first 4-12 weeks of therapy

and may be related to expansion of plasma volume.[1] Pioglitazone is not indicated in heart failure patients with NYHA III or IV cardiac status. In clinical trials, weight gain was associated with pioglitazone therapy (0.5 to 3.7 kg), with the greatest increase when used in combination with insulin (2.3 to 3.7 kg). Pioglitazone may cause resumption of ovulation in anovulatory patients with insulin resistance. Contraceptive measures should be considered in these patients. Ketoconazole may inhibit the metabolism of pioglitazone by inhibiting cytochrome P450 isoform 3A4.[1]

Comments

Pioglitazone is the third thiazolidinedione to be approved. Results from clinical trials (16-26 weeks in duration) have not been published. Limited details are available from the manufacturer and abstracts.[1,2,3,4,5,6] As monotherapy (n = 865), pioglitazone produced a mean reduction in fasting blood glucose of 30-56 mg/dL from baseline (267-281 mg/dL) and reduction in glycosylated hemoglobin (HbA1c) from 0.3 to 0.9% (10.2-10.8%).[1,2,3] In combination with a sulfonylurea (n = 560) or metformin (n = 328), pioglitazone produced a mean reduction in fasting blood glucose of 34-58 mg/dL from baseline (236-259 mg/dL) and 0.8-1.3% reduction (9.8-10%) in HbA1c.[1,4,5] In combination with insulin (n = 566), pioglitazone produced reductions of 35-49 mg/dL in fasting blood glucose and 0.7-1% in HbA1c.[1,6] A greater HbA1c reduction has been observed in female patients than in male patients (mean difference of 0.5% in HbA1c).[1]

Clinical Implications

Thiazolidinediones are the newest class of antihyperglycemic drugs, providing a different mechanism of action from the sulfonylureas, metformin, insulin, and alpha-glucosidase inhibitors (acarbose, miglitol). As monotherapy, the magnitude of the glycemic control achieved with thiazolidinediones is generally less than that seen with sulfonylureas or metformin, making them more suitable for combination therapy. Due to the natural progressive course of type 2 diabetes, combination therapy is usually unavoidable. In the first three years of treatment, about 50% of patients achieve control with monotherapy but this is reduced to only 25% after nine years.[7]

Troglitazone had wide appeal as a combination drug until reports of drug-induced hepatotoxicity associated with the drug forced it off the market in Europe and led the FDA to impose strict monitoring of liver function tests in this country. Both pioglitazone and rosiglitazone are touted as being safer than troglitazone, as drug-induced hepatotoxicity has not been reported in clinical trials. The two drugs also seemed to be similar in efficacy (the magnitude of reduction in fasting plasma glucose and glycosylated hemoglobin) and in their side effect profiles (e.g., edema, weight gain). Their effect on the lipid profile may offer a point of differentiation. While both drugs increase HDL-cholesterol (7-8 mg/dL), rosiglitazone increased LDL-cholesterol more than pioglitazone (10-15 mg/dL to 5 mg/dL). In addition pioglitazone reduced triglyceride levels by about 50 mg/dL while rosiglitazone had no effect.[8] Since these differences are not from direct comparative studies, the exact magnitude of the difference and clinical significance remains to be determined.

Pioglitazone is priced between $2.85 and $4.95 per day, similar to rosiglitazone. ❖

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CME Questions

36. Angiotensin receptor blockers are clearly indicated for:

a. heart failure.
b. post-myocardial infarction.
c. diabetic nephropathy.
d. hypertension.

37. Partial tears of the ACL involving less than 50% of the ligament:

a. progress to complete tears in most cases.
b. rarely progress to complete tears.
c. frequently result in late arthritic changes.
d. significantly limit patients' activities over time.

38. With regard to Pioglitazone tablets, no evidence of drug-induced hepatotoxicity or elevation of ALT levels has been reported.

a. True
b. False

By Louis Kuritzky, MD

Bed Rest: A Potentially Harmful Treatment Needing More Careful Evaluation

Generations of healers have believed in the therapeutic benefits of bed rest, including commentary by Hippocrates himself. Through the 1800s, with few efficacious tools at hand, bed rest was a primary treatment for many disorders. Contrary to this time-honored wisdom, consequences like DVT, osteoporosis, pressure sores, contractures, and atrophy have all been ascribed to bed rest. Only a few areas of medicine have specifically examined the role of bed rest as a therapeutic modality.

Allen and colleagues were able to identify 39 randomized trials referable to 15 different disorders such as bed rest for post-lumbar puncture, radiculography, cardiac catheterization, liver biopsy, low back pain, labor, threatened abortion, myocardial infarction, and rheumatoid arthritis.

Among 24 trials of bed rest after a medical procedure, none demonstrated significantly improved outcome, though a number did show statistically significantly worse outcome. Even in trials of spinal headache post-lumbar puncture, no significant benefit of bed rest was discernible. No benefit of bed rest is demonstrated for acute low back pain, myocardial infarction, tuberculosis, or hepatitis. Similarly, obstetrical trials not only show no improvement when bed rest is employed in first-stage labor, they actually show worse outcomes.

That bed rest is of questionable value has not seemed to effect change among clinicians. Seventeen years after the publication of a trial on the absence of benefit from bed rest after lumbar puncture, 80% of neurologists in the United Kingdom continued to insist upon the practice. Scientifically substantiated indications for bed rest remain to be defined. ❖

Allen C, et al. Lancet 1999;354: 1229-1233.

Exogenous Reinfection as a Cause of Recurrent Tuberculosis After Curative Treatment

Tuberculosis occurring many years after primary infection is called postprimary TB. Previous to the availability of DNA fingerprinting, it was unclear whether postprimary TB was a consequence of reactivation of endogenous primary disease or reinfection, though traditional opinion held that endogenous reactivation was the primary method. With currently available tools, it is now possible to discern whether postprimary TB is caused by the same strain that was etiologic for the primary infection or another strain.

The population studied, from Cape Town, South Africa, reflects a high number of cases of TB per year (1000 cases per 100,000 population per year). Subjects sustained at least two episodes of postprimary TB within a six-year period. These patients were all HIV negative, free from diabetes, end-stage renal disease, or other immunosuppressive disorder.

A different DNA pattern than had been causative of the primary infection was reported in 75% of postprimary TB cases. Twenty-five percent of postprimary TB involved drug-resistant strains, of which half were due to exogenous reinfection and half due to endogenous reactivation.

Since, in this population, most postprimary TB is a result of exogenous reinfection, van Rie and colleagues suggest additional emphasis on early case detection to prevent exposure to active disease in those with cured primary TB. It is unknown whether these data will be reflective of post-primary TB etiologies in settings with less prominent background disease rates, where opportunity of exposure to new active cases is substantially less. ❖

van Rie A, et al. N Engl J Med 1999; 341:1174-1178.

HIV-1 Drug Resistance in Newly Infected Individuals

As many as half of hiv-1 infected individuals treated with antiviral therapy may develop resistance. Contributing factors include serial monotherapy, uninhibited viral replication due to inadequate suppression by less than maximally effective agents, difficulty adhering to complicated regimens often associated with substantial burden of side effects, and therapy begun late in the course of the disease. Transmission of multidrug-resistant HIV-1 virus is a serious concern. To evaluate the demographics of this problem, Boden and associates evaluated mutations in 80 newly HIV-1 infected individuals who acquired the disease between July 1995 and April 1998; during this time, multidrug treatment of HIV had become the standard methodology.

More than 16% of samples analyzed demonstrated resistance to one or more antiretroviral agents and almost twice that number showed a three-fold or greater reduction in susceptibility to at least one retroviral agent. Only about 4% of samples demonstrated multidrug resistance.

Study subjects in this group came primarily from a population of urban homosexual men. Hence, demographics here described may not reflect other community settings and may not be applicable to women or heterosexual men. Boden et al suggest that clinical trials that evaluate potential virological and immunological benefits achieved by using resistance assay-guided therapeutic regimens are in order. ❖

Boden D, et al. JAMA 1999;282: 1135-1141.

Lead Misplacement and Chest Pain?

By Ken Grauer, MD

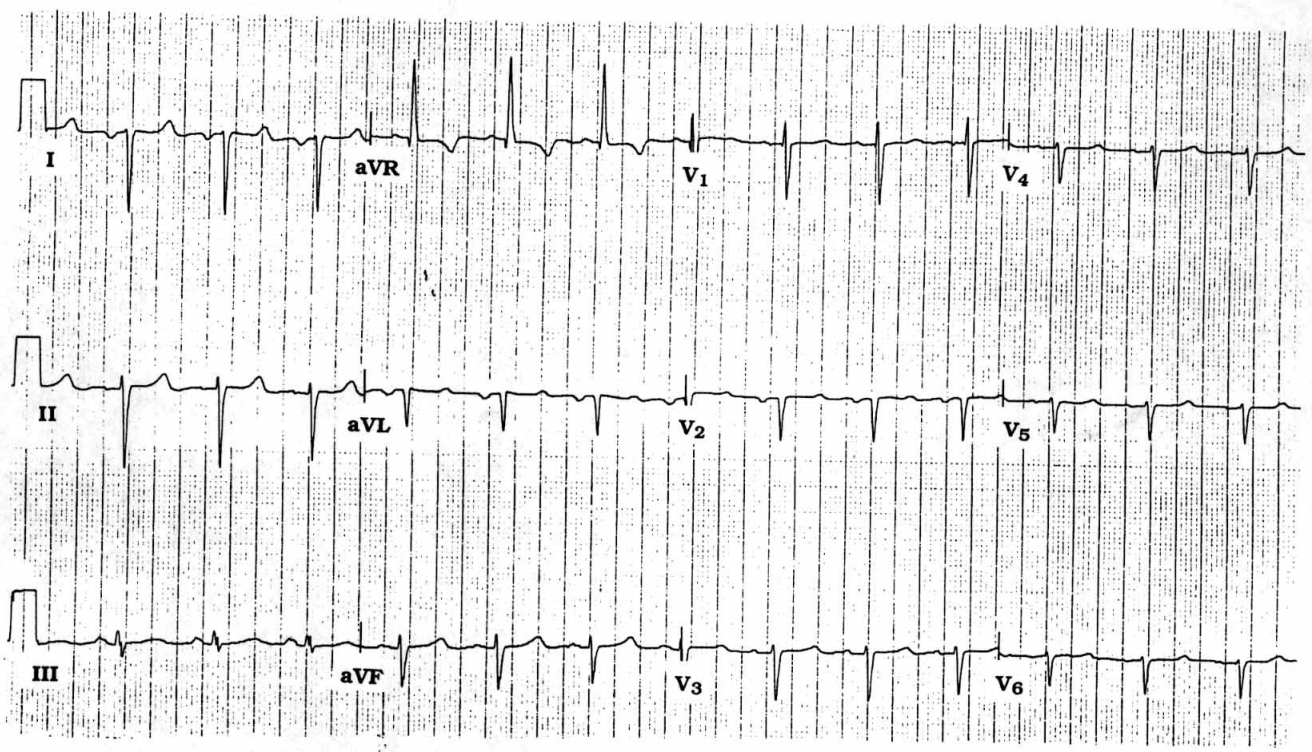

Figure. ECG obtained from a 60-year-old woman with chest pain. Is there lead misplacement?

Clinical Scenario: The ECG shown in the Figure was obtained from a 60-year-old woman with chest pain. As was the case for the last month's ECG Review (*Intern Med Alert* 1999;21:168), the QRS complex is predominantly negative in lead I and positive in lead aVR. Is this another case of lead misplacement? Is there any additional information that can be surmised from this tracing?

Interpretation: The ECG in the Figure is unusual in several ways. The rhythm is regular at a rate of about 80 beats/minute, but the nature of atrial activity is uncertain. That is, although an upright P wave is clearly seen and obviously conducting (constant PR interval) in lead III—no definite P wave is seen in lead II.

The most common form of lead misplacement results from interchange of the left and right arm electrodes. This technical mishap produces a picture of global negativity (of P wave, QRS complex, and T wave) in lead I—and an upright complex in lead aVR. However, limb lead misplacement should *not* affect QRS morphology in the precordial leads, since chest lead placement is not changed in any way. The Figure in this case shows a precordial lead pattern consistent with *reverse* R wave progression (small r wave in lead V_1 that gets even smaller as one approaches lead V_6). This strongly suggests that this patient has true dextrocardia, a finding confirmed on physical examination and repeat ECG. The unusual finding about this dextrocardia tracing is that instead of global negativity in lead I, the T wave is peaked and *upright*—a subtle finding suggesting ischemia as the cause of her chest pain. ❖

In Future Issues: Interruption of the Renin-Angiotensin Access