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Cost-Utility of Three Approaches to Sleep Apnea: Polysomnography, Home Testing, Empirical Therapy

ABSTRACT & COMMENTARY

Synopsis: *The advantage gained by polysomnography over other approaches was comparable to that of other procedures like coronary artery bypass surgery, dialysis, and screening asymptomatic patients for carotid artery stenosis.*

Source: Chervin RD, et al. *Ann Intern Med* 1999;130:496-505.

Obstructive sleep apnea syndrome (osas) occurs with repeated obstruction of breathing during sleep and is associated with daytime sleepiness, significant cardiovascular morbidity, and increased mortality. Recent data suggest that 2-4% of adults have this disorder. Nasal continuous positive airway pressure (NCPAP) is the most commonly used treatment and has a favorable cost-utility ratio. However, OSAS remains undiagnosed in at least 82% of men and 93% of women with the condition. The gold standard for the diagnosis of OSAS is nocturnal polysomnography, but this is associated with significant expense, at a cost of $1000-1400 per patient. Some investigators have suggested that sleep apnea can be diagnosed with either a home study or by clinical symptoms and physical finding alone at a much lower cost, albeit with less accuracy. The present study was conducted to compare the cost-effectiveness of these strategies using decision analysis techniques.

Chervin and associates first constructed a decision tree in which a hypothetical adult with OSAS was evaluated and treated. Within the decision tree, three alternative approaches to diagnosis were used, chances of positive or negative test results were considered, the possibilities of treatment with or without NCPAP were entered, the probability that OSAS was actually present was entered, and the resulting health state was considered. The data used in the tree were derived from consecutive, sleep center-referred, adult case series with the diagnosis of OSAS. On average, the patients modeled were in the sixth decade of life, most were males, and many had cardiovascular comorbidity.

Outcome measures included the quality-adjusted life years

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INSIDE

(QALY) (utility × expected life span) for the first five years (QALY 5) and incremental cost. A decision analysis was used to determine the magnitude of the advantage afforded by the best diagnostic approach—polysomnography, home study, or no testing—measured in QALY 5. Also, five-year incremental cost-utility ratios in U.S. dollars of obtaining that advantage were calculated. After derivation of results of a base case, a univariate sensitivity analysis was done to test the effects on the model of different but plausible utilities, survival rates, pretest probabilities of OSAS, test characteristics, and costs. Baseline utilities of four possible health states (outcomes), mean survival during five-year period after diagnostic evaluation and resulting QALY were calculated. QALY were: 4.104 for patients with OSAS using NCPAP; 2.972 for patients using NCPAP without OSAS; 2.804 for patients with OSAS not using NCPAP; and 3.538 for patients without OSAS and not using NCPAP. Mean survival during the five-year period was 5, 5, 4.7, and 5 years, respectively.

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An Eden trace model 2700 with a sensitivity and specificity of 0.95 and 0.96 (respectively) in polysomnographically proven OSAS was used in the model. The proportion of all home studies expected to yield positive results was calculated to be 0.81. In no test branch did all patients with OSAS receive treatment.

Charges as a proxy of cost were used to calculate the incremental cost. The average total charge for patients in any given branch of the decision tree was calculated, including five-year total charges for any tests, office visits, and NCPAP setups, along with the probability that each charge would be incurred. Charges after the first year were discounted at the rate of 3% per year including the future utilities. In a baseline decision analysis, polysomnography generated higher QALY 5 (4.019) and diagnostic and treatment charges ($4210) than home study (3.955 and $3460, respectively) and no testing (3.934 and $3020, respectively). The incremental cost-utility ratio for polysomnography compared with home study and no testing were $13,431 and $9165, respectively, per QALY gained.

A multivariate analysis was then done to recalculate the cost-utility ratios under the assumption that the frequency of OSAS was only 0.35 and that the charge for a home study was only $50. Under these assumptions, the cost-utility ratio for polysomnography compared with home study increased to $30,070 per additional QALY 5 gained by polysomnography if the sensitivity and specificity of the test remained at 95% and 96%, respectively. The cost-utility ratio would decrease to $40,000 if the sensitivity and specificity dropped to 80% and 70%, respectively.

COMMENT BY DAVID OST, MD

Because of increasing awareness of OSAS among physicians and the lay public, the importance of accurate diagnosis and treatment is increasing. Almost every insurance company reimburses for standard overnight polysomnography for the diagnosis of OSAS. Because of its expense (one night polysomnography costs approximately $1000-4000), other inexpensive diagnostic modalities are being used in clinical practice, including home studies. These studies are cheap and easy to use, but their overall effect on making an accurate diagnosis and long-term costs is still questionable. The present study was conducted to determine the cost-utility of three approaches to OSAS: polysomnography, home testing, and empirical therapy.

Chervin et al demonstrate that formal polysomnography results in an improved quality of life at a cost that is comparable to and less than many other well accepted therapeutic interventions. Importantly, this result was true over a wide range of potential values for sensitivity,

specificity, and prevalence of disease. This study provides important information to the clinician for evaluating the many patients with possible OSAS. Cheaper but less accurate home tests may not be better. Clearly, this study may also have a tremendous effect in terms of public health policy and financing. ❖

Is Angioplasty Needed in Stable CAD or Will Aggressive Lipid-Lowering Therapy do as Well?

ABSTRACT & COMMENTARY

Synopsis: *It would appear that lipid-lowering therapy should be considered in all patients with known coronary artery disease, perhaps even regardless of what the cholesterol, LDL, and HDL levels are at the time of the initiation of therapy.*

Source: Pitt B, et al, for the Atorvastatin vs. Revascularization Treatment Investigators. *N Engl J Med* 1999;341:70-76.

There is certainly no question that percutaneous transluminal coronary angioplasty (PTCA) has been an effective form of treatment of patients afflicted with symptomatic coronary artery disease (CAD) ranging all the way from stable angina pectoris to acute myocardial infarctions. The numerous studies that have compared medical therapy with PTCA in patients with symptomatic CAD have suggested that PTCA was more effective than standard medical therapy in improving the quality of life and exercise performance.[1-3] On the other hand, lipid-lowering therapy has been demonstrated to significantly reduce the incidence of overall cardiovascular mortality, overall cardiovascular events, and the need for revascularization procedures.[4,5]

Pitt and colleagues recently reported the results of a randomized, controlled, multicenter study comparing the outcomes of patients who received usual medical treatment and a lipid-lowering agent (atorvastatin) with the outcomes of matched patients who were first subjected to PTCA (with or without stenting) and who then received usual medical treatment including lipid-lowering therapy. This 18-month open-labeled study was performed in 341 patients with stable CAD, normal left ventricular function, asymptomatic or mild-moderate angina pectoris, and a serum level of low-density lipoprotein cholesterol (LDL) of at least 115 mg/dL who were referred for PTCA. The results demonstrated that the incidence of ischemic events was 36% lower over an 18-month period in the atorvastatin without PTCA group, but these results were not statistically significant after the reduction in events were adjusted because of the smaller number of angioplasty procedures, coronary artery bypass operations, and hospitalizations for worsening angina that occurred in the atorvastatin group. However, it should be noted that the medically treated patients had had a significantly longer period of time to a first ischemic event (P = 0.03) than did patients who were subjected to PTCA/usual care.

COMMENT BY HAROLD L. KARPMAN, MD

Pitt et al have carefully evaluated the results obtained from the 37 medical centers in North America and Europe who participated in this study and have clearly demonstrated a 46% reduction in LDL levels in the atorvastatin group compared to an 18% reduction of LDL levels in the PTCA and usual care group; in addition, the total serum cholesterol was reduced by 37% and 10%, respectively. The mean level of LDL cholesterol was 77 mg/dL in the study group and 119 mg/dL in the PTCA/usual care group.

Even though the 36% lower incidence of ischemic events over a period of 18 months in patients treated with atorvastatin narrowly missed the level of significance after being adjusted, the final results must be considered to be most important. This is especially true because of the significantly longer time to a first ischemic event that was noted to occur in patients treated with atorvastatin when compared to the PTCA group (i.e., P = 0.03). Previous trials have suggested that the beneficial effects of lipid-lowering therapy become apparent after six or more months of therapy;[4,5] a similar time delay to the onset of measurable benefits was noted in the Pitt study suggesting that these benefits occurred because of the lowering of serum lipid levels with atorvastatin. It should be recognized that a longer follow-up period would not likely demonstrate a convincingly greater benefit of angioplasty compared to lipid-lowering therapy since in most lipid-lowering trials, there has been little benefit of lipid-lowering therapy over placebo in the first two years of treatment after which time significant improvement occurs and outcome curves begin to diverge. In summary, it would appear that aggressive lowering of serum lipids is likely to diminish or prevent further progression of minimal to moderate CAD lesions and, thereby, prevent plaque rupture.[6]

It should be carefully recognized that this study does not provide evidence with respect to the relative value of PTCA vs. medical therapy in patients who have severe or acute symptomatology, whose quality of life has been severely affected, and/or in high-risk patients with left

ventricular dysfunction, left main CAD and/or triple vessel disease, or in patients with severe angina with diminished exercise tolerance. Additional long-term trials will be required to determine whether aggressive lowering of lipid levels will compliment angioplasty in such patients by stabilizing coronary arterial lesions; however, for the time being, this paper would suggest that pharmaceutically induced lipid-lowering appears to be as safe and effective as PTCA/usual medical care in reducing the incidence of ischemic events. And, of course, if at any time symptoms were to increase or exercise performance were to deteriorate to the point where these events were to interfere with a patient's quality of life, physicians might at that time elect to have their patients undergo revascularization with only minimal (if at all) additional risk having been incurred because of their initial decision to pharmacologically treat the patient.

Numerous studies have suggested that cholesterol lowering should be extended to patients with acute coronary conditions and that we should hasten to initiate this form of therapy rather than withholding drug therapy in order to see whether diet therapy alone will be effective in controlling the serum lipid values. Currently mounted clinical trials should soon define with certainty whether cholesterol lowering should play a role in the treatment of all patients with unstable angina and myocardial infarctions because cholesterol lowering may have immediate consequences that favorably affect coronary events. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial is currently randomizing 3000 patients with unstable angina or non-Q-wave myocardial infarction to atorvastatin or placebo beginning during the acute hospitalization and continuing for 16 weeks of follow-up. Another trial currently in the final stages of protocol development will test the effects of early vs. delayed simvastatin therapy in 4500 patients with acute coronary syndromes followed for one year. Whether the outcomes of these acute treatment trials will affect long-term therapy (i.e., drugs vs PTCA vs surgery) will almost certainly become apparent within the next several years but again, for the time being, it would appear that lipid-lowering therapy should be considered in all patients with known CAD, perhaps even regardless of what the cholesterol, LDL, and HDL levels are at the time of the initiation of therapy.[7,8] ❖

References

1. Parisi AF, et al. *N Engl J Med* 1992;326:10-16.
2. Hueb WA, et al. *J Am Coll Cardiol* 1995;26:1600-1605.
3. *Lancet* 1997;350:461-468.
4. Scandinavian Simvastatin Survival Study Group. *Lancet* 1994;344:1383-1389.
5. Sacks FM, et al. *N Engl J Med* 1996;335:1001-1009.
6. Waters D. *Prog Cardiovasc Dis* 1994;37:107-120.
7. Waters D. *Circulation* 1999;99:3215-3217.
8. Dupuis J, et al. *Circulation* 1999;99:3227-3233.

Can Diet and Monotherapy Maintain Fasting Blood Glucose and HbA1c at Levels Recommended by the ADA?

ABSTRACT & COMMENTARY

Synopsis: *After nine years, only 25% of the patients in the UKPDS 49 could maintain blood glucose and HbA1c levels recommended by the American Diabetes Association.*

Source: Turner RC, et al. *JAMA* 1999;281:2005-2012.

The united kingdom prospective diabetes study (UKPDS 33) has previously confirmed that improved blood glucose control will delay the progress of microvascular complications in patients with type 2 diabetes mellitus.[1] The objective of UKPDS 49 was to assess how often various monotherapies and diet alone can achieve the glycemic control targets set by the American Diabetes Association (ADA). (HbA1c levels < 7% and fasting blood glucose [FBG] levels < 140 mg/dL.)

A total of 4075 patients newly diagnosed as having type 2 diabetes mellitus ranging from 25-65 years in age, with a median FBG concentration of 207 mg/dL and a HbA1c level of 9.1%, and who had a mean body mass index of 29 constituted the study group.

After three months on a high carbohydrate, high-fiber diet patients were randomized to therapy with diet alone, insulin, sulfonylureas, or metformin. Each therapeutic agent as monotherapy increased two- to three-fold the proportion of patients who attained a Hba1c level below 7% compared to diet alone. However, the progression of deterioration was such that after three years, approximately 50% of patients could attain this goal with monotherapy, and after nine years this declined to 25%. The majority of the patients need multiple therapies to attain these target levels in the longer term.

COMMENT BY RALPH R. HALL, MD, FACP

It is now deemed important to reach the goals recommended by the ADA since attaining these goals is associated with a marked reduction of microvascular disease. Until now, physicians have avoided multiple drugs hoping to enhance compliance and quality of life. Their

patients, however, had HbA1c levels far above the recommended goals.

The situation becomes even more complicated if the patients have hypertension and elevated blood lipids. UKPDS 39[2] demonstrated that if recommended levels of blood pressure were to be attained, three drugs would be necessary in at least 29% of the patients. Another recent study has shown that only 66% of the patients reach recommended goals for blood lipids when two drugs are used in maximum dosages.[3]

What is the solution? UKPDS 33 also demonstrated that insulin was not harmful. Perhaps we should use insulin with one other oral drug. Insulin has been shown to work well with metformin. However, metformin usually requires two or more tablets per day when the long-acting sulfonylureas require only one tablet per day. We should strive to use the most powerful of the statin drugs for management of blood lipids and try to increase exercise intensity to a greater degree than we have in the past. Exercise has been successful in lowering both blood glucose and blood lipids and, if used 4-5 times per week, to be effective in weight reduction, which has its own benefits.

There are both short-term quality of life issues (the inconvenience of taking multiple drugs) and long-term quality of life issues, such as the development of microvascular disease and macrovascular disease, to consider.

Until we have better drugs or can have better compliance with weight reduction and exercise, we will need to spend more time with our patients working on both short- and long-term quality of life issues. ❖

References

1. UKPDS 33. *Lancet* 1998;352:837-853.
2. UKPDS 39. *Br Med J* 1998;317:713-720.
3. Kanters SDJM. *Diabet Med* 1999;16:500-508.

Pharmacology Update

Zanamivir for Inhalation (Relenza—Glaxo Wellcome)

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

Just in time for the 1999 flu season, the fda has approved Glaxo Wellcome's zanamivir (Relenza) for the treatment of influenza A and B. Zanamivir is the first of a new class of antiviral drugs, the sialic acid analogs, which were developed through computer-assisted design. These drugs are believed to inhibit viral replication by inhibiting the viral surface enzyme, neuraminidase.[1] Zanamivir is formulated as an inhaled product that is delivered through a breath activated device.

Indications

Zanamivir is indicated for the treatment of uncomplicated acute illness due to influenza virus (A and B) in adults and adolescents (≥ 12 years of age). Patients should be symptomatic for two days or less.[2]

Dosage

The recommended dose is two inhalations at 5 mg each twice daily, about 12 hours apart, for five days. Two doses should be administered on the first day of treatment (at least 2 hours apart). Treatment should be initiated within two days after onset of symptoms. Patients should be instructed in the proper use of the delivery device and advised to complete the five-day course.[1]

Zanamivir is supplied as powder for inhalation. Each foil pack contains four blisters—each contain 5 mg of zanamivir and 20 mg of lactose. The contents of each blister is inhaled using a Diskhaler.

Potential Advantages

In contrast to amantadine and rimantadine, which are effective against influenza A only, zanamivir is active against influenza A and B although in the clinical trials patients were predominately infected with influenza A.[1] The drug is well tolerated and is generally free of systemic side effects.[2-4] One placebo-controlled study (n = 455) conducted in Australia, New Zealand, and South Africa reported a significant reduction in median time to the symptom relief of 1.5 days (6.0-4.5 days) in patients who initiated therapy within 36 hours of onset based on intent-to-treat analysis. In patients who were influenza positive and febrile, the median reduction was two days (6.5-4.5 days).[3] A small number of high-risk patients (n = 79) had a statistically significant reduction in median time to alleviation of symptoms of 2.5 days (8.0-5.5 days).[3] In influenza-positive patients, zanamivir-treated patients also reported less sleep disturbance and earlier return to normal activity.[3]

Potential Disadvantages

The administration of the drug requires two inhalations of zanamivir powder twice daily. The FDA had some concerns that this delivery system may be cumbersome for some patients and may require some initial training. Patients with underlying respiratory disease may experience bronchospasm and/or decline in pulmonary function after use of the drug.[2] These patients should have a short-acting beta agonist available when treated with zanamivir.[2] Therapy should be initiated within 48 hours after onset of influenza symptoms, and preferably within 36 hours.

Comments

Zanamivir is the first of a new class of antivirals, the selective neuraminidase inhibitors. Neuraminidase, also referred to as sialidase, is a surface glycoprotein essential for the replication of both influenza A and B viruses.[5] The speculated roles of this enzyme include promotion of the release of virions from infected host cells, prevention of viral inactivation by respiratory mucus, and inducing the elaboration of certain cytokines (e.g., tissue necrosis factor).[5] Animal models indicated that zanamivir reduces viral replication.[1] The clinical benefit of zanamivir is modest. In a study conducted in the Southern Hemisphere (n = 455), zanamivir reduced the median time to symptom relief by 1.5 days when patients initiated treatment within 36 hours.[3] However, in studies conducted in North America (n = > 600), zanamivir reduced the median time to symptom relief by only one day when patients initiated treatment within 48 hours and statistical significance was not achieved.[2] Time-to-symptom improvement was defined as improvement in major symptoms: resolution of fever, headache, myalgia, cough, and sore throat.[2] Findings from clinical trials did not show any difference in the rate of development of complications between treatment groups. The drug has not been adequately studied in patients with high-risk underlying medical conditions. Zanamivir is currently FDA approved for the treatment of uncomplicated acute illness due in influenza. It is not approved for the prevention of illness, although a recent randomized, controlled trial showed the drug to be efficacious in healthy young adults.[4]

Zanamivir-resistant strains have been isolated in vitro; however they have been reported to be less infectious.[1,2,7] The wholesale cost for a treatment course of zanamivir (5 days) is $44.

Clinical Implications

Prior to the approval of zanamivir, only amantadine and rimantadine have been approved for the treatment of influenza. The use of these agents was limited by inactivity against influenza B, rapid development of resistance, and CNS and gastrointestinal side effects. In contrast, zanamivir is active against influenza A and influenza B. It is well tolerated but should be used with caution in patients with underlying respiratory disease. Drug-resistant viruses can appear in about one-third of patients treated with amantadine or rimantadine.[6] In clinical trials of zanamivir, drug-resistant strains have not been a problem.[1,4] The benefit of zanamivir is modest. North American data showed that initiation of therapy within 48 hours failed to produce a statistically different reduction in median time to symptom improvement. Initiation of therapy within 36 hours may improve the efficacy, although it is unlikely that most adults will seek medical care or receive a definative diagnosis of influenza within 36 hours of onset of symptoms. The delivery system may also represent an obstacle to appropriate use in early stages of the illness. An orally active neuraminidase inhibitor is currently in the FDA pipeline.

There are no indications that the drug can reduce complications of influenza illness in patients at risk for these events. Vaccination remains the primary prophylactic means of controlling influenza and preventing sequelae. Patients should not eschew vaccination in favor of treatment after infection. The chemoprophylactic use of zanamivir has not been FDA approved, but neuraminidase inhibitors, especially orally active ones, may eventually have a role in managing influenza outbreaks particularly involving variant strains not covered by the vaccine. ❖

References

1. Waghorn SL, et al. *Drugs* 1998;55(5):721-725.
2. Relenza Product Information. Glaxo Wellcome Inc. July 1999.
3. MIST Study Group. *Lancet* 1998;352:1877-1881.
4. Monto AS, et al. *JAMA* 1999;282(1):31-35.
5. Calfee DP, et al. *Drugs* 1998;56(4):537-553.
6. *Morb Mortal Wkly Rep MMWR* 1999;48:15-23.
7. Tai CY, et al. *Antimicrob Agents Chemother* 1998; 42:3232-3241.

Correction

Due to an American Health Consultants error, the dosage information in the Pharmacology Update on Rosiglitazone (*Intern Med Alert* 1999;21:110) is incorrect. The sentences should have read: "The recommended starting dose for rosiglitazone is 4 mg daily administered qd or bid. . . . The difference in glycosylated hemoglobin was significantly greater with 8 mg qd vs. 4 mg bid but not statistically different at 4 mg qd vs. 2 mg bid." We regret any confusion this may have caused. ❖

CME Questions

18. After three years, what percent of the patients in the UKPDS study were controlled on monotherapy?

a. 75%
b. 50%
c. 25%
d. 85%

19. Which of the following statements about zanamivir is *not* true?

a. It should be started as early as possible.
b. It is approved for preventing influenza.
c. It is an oral inhaler.
d. It treats influenza A and B.

By Louis Kuritzky, MD

Gemfibrozil for CAD in Men with Low Levels of High Density Lipoprotein Cholesterol

Up to 30% of patients with coronary disease have a low level of HDL as their primary abnormality, with normal levels of LDL cholesterol. Clinical trials have generally focused upon persons with elevated LDL cholesterol and have proven that lowering LDL below 130 with pharmacotherapy reduces major cardiac events.

The Veterans Affairs HDL Cholesterol Intervention Trial Study Group investigated treatment with gemfibrozil in men with low HDL (< 40 mg/dL) and normal LDL (< 140 mg/dL); all men had proven coronary heart disease (n = 2531).

On average, treatment lasted about five years. Treatment was associated with a 22% relative risk reduction in cardiac events, designated as combined incidence of nonfatal MI and fatality due to coronary heart disease. The combination of death from coronary heart disease, nonfatal MI, and stroke was also reduced 24%. These effects were achieved with a mean reduction in cholesterol of 4%, triglyceride 31%, and a 6% increase in HDL. Treatment had no effect on LDL in these patients, with baseline LDL less than 140.

The only common side effect attributed to gemfibrozil was dyspepsia, for which there was a placebo-subtracted frequency of 6%. All other measured adversities were equivalent for the active treatment and placebo group.

This study concludes that for patients whose primary lipid abnormality is low HDL, secondary preventive treatment with gemfibrozil reduces MI and death from coronary heart disease. ❖

Rubin HB, et al. N Engl J Med 1999; 341:410-418.

Contact Lens-Associated Microbial Keratitis

Most of the 28 million contact lens wearers in the United States use them for cosmetic reasons as an alternative to spectacles for correcting refractive errors, as opposed to the small number (3%) who use them for treatment of ocular surface diseases or aphakia. Microbial keratitis, which may result in permanent corneal scarring or perforation, with subsequent permanent visual loss, is the most dreaded complication of contact lens wear. It is usually due to bacteria, though fungi and acanthamoebae have also been implicated.

For this study, a prospective population study was done among all ophthalmologists in the Netherlands (n = 440), who were asked to report all cases of microbial keratitis seen over a 90-day period in 1996. During this interval, 111 cases of keratitis were identified.

Extended wear soft contact lens (1-2 week disposables) users were almost 20 times as likely to incur microbial keratitis as users of daily-wear rigid gas-permeable lens users. Even daily-wear soft lenses were more than three times more likely to suffer microbial keratitis than rigid gas-permeable lens users. In this trial, *Serratia* and *Pseudomonas aeruginosa* were the most commonly isolated bacteria; only one case of acanthamoeba was identified, and there were no fungal infections. Less than half of all cases had any pathogen recoverable from culture.

Infections resulted in five hospitalizations, requiring one excimer laser corneal scar excision and three cases of corneal transplantation due to visual impairment from scar. The patient with acanthamoeba progressed to visual impairment resulting in near-blindness.

Cheng and colleagues note that overnight use of lenses was the primary risk factor for corneal infection and should hence be discouraged. In this population, rigid gas-permeable lenses were associated with the least risk of microbial keratitis. ❖

Cheng KH, et al. Lancet 1999;354: 181-185.

ACE-Inhibition in Nondiabetic Nephropathies

Prevention of overt nephropathy by treatment of proteinuria with ACE inhibitors is well established for patients with diabetes. A 1997 trial of ACE inhibitor therapy (ramipril) for hypertensive nondiabetic patients with significant nephropathy (protein excretion > 3 g/d) was so successful that the trial was stopped early. Another subgroup of this same population, consisting of persons with more modest levels of proteinuria (between 1-3 g proteinuria daily) was the subject of this investigation.

Study participants (n = 175) were normotensive or hypertensive and had persistent proteinuria. After a median of 31 months treatment with the ramipril, significantly fewer treated patients progressed to end stage renal failure or to overt proteinuria. Patients with the lowest baseline renal function (GFR 45 mL/min or less) demonstrated the greatest therapeutic benefits. As anticipated, the decline in renal function in this study was that of the preceding trial that had included more severe proteinuria. Overall, patients with proteinuria cut their risk of progression to end stage renal failure and severe proteinuria in half.

Ruggenenti and colleagues note that since proteinuria greater than 3 g/24/h heralds rapid progression of renal deterioration, clinicians should aim to forestall this degree of proteinuria. They also suggest that the commonplace practice of withholding ACE inhibitors in severe renal failure for fear of further failure or hyperkalemia is not justified. ❖

Ruggenenti P, et al. Lancet 1999;354: 359-364.

Irregular VT?

By Ken Grauer, MD

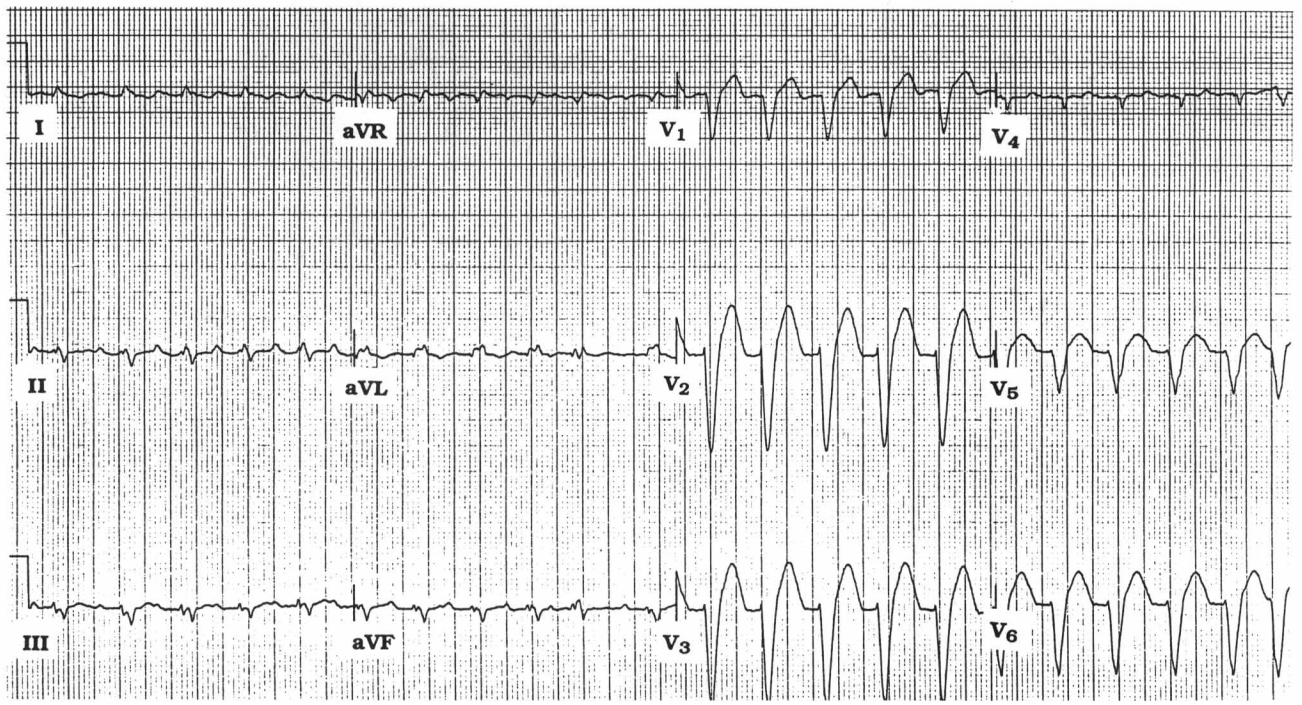

Figure. 12-lead ECG obtained from a woman with coronary disease. Is this VT?

Clinical Scenario: The ECG shown in the Figure was obtained from a woman in her 60s with known coronary disease. In view of the fact that ventricular tachycardia (VT) *may* sometimes be slightly irregular, would you interpret the rhythm in this Figure as probable VT?

Interpretation: The rhythm in the Figure is a fairly regular, wide-complex tachycardia. Whenever this is seen in an older adult with known coronary disease—VT must *always* be assumed until proven otherwise, especially when QRS morphology looks as bizarre as it does in this tracing. That said—the cause of the wide complex tachycardia in the Figure is *not* VT. As is often the case—the key clue for interpreting this rhythm lies with "looking for a pause"!

Whereas on initial inspection one might not think any P waves at all are present on this tracing, the brief pause preceding the last beat in lead aVF strongly suggests otherwise. A P wave clearly precedes this last beat in lead aVF with a normal PR interval. Looking again at lead II, it can now be seen that the second QRS complex in this lead is also preceded by a P wave with a similar PR interval as the last beat in lead aVF. The small upright deflection at the midpoint of the R-R interval for the other beats in lead II is therefore *not* a T wave, but instead represents sinus node activity. Therefore, the rhythm in this tracing is sinus tachycardia with several premature supraventricular beats (PACs or PJCs)—and QRS widening as the result of an unusual form of IVCD (intraventricular conduction delay). We emphasize that without the pauses in the rhythm described above, one would have to assume VT for this tracing. ❖

In Future Issues: **Pharmacology Update: Rabeprazole (Aciphex)**