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## INSIDE



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# COPD, PE, or Both?

ABSTRACT & COMMENTARY

***By Allan J. Wilke, MD***

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*Dr. Wilke reports no financial relationship to this field of study.*

***Synopsis:*** *Pulmonary embolism occurs commonly in patients with unexplained exacerbations of chronic obstructive pulmonary disease.*

**Source:** Tillie-Leblond I, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med*. 2006;144:390-396.

THE SYMPTOMS OF PULMONARY EMBOLISM (PE) AND ACUTE exacerbation of chronic obstructive pulmonary disease (COPD) overlap one another at the intersection of worsening dyspnea and hemoptysis. Tillie-Leblond and colleagues from the Lille University Hospital set out to determine the presence of PE in patients with acute exacerbation of COPD of unknown origin. In addition, they looked for factors that are associated with PE in COPD.

Two hundred eleven (211) consecutive patients with COPD as defined by the American Thoracic Society (ATS), who were referred to the Lung Department with severe exacerbation of undetermined origin, were eligible for inclusion in the study. Exclusion criteria included patients with asthma, lower respiratory tract infection, pneumothorax, or lung consolidation, and those needing intubation and ventilation. All patients underwent spiral computerized tomographic angiography (CTA) of the lungs and color Doppler and venous ultrasonography (US) of the legs. D-dimer and ventilation-perfusion scans were performed at the attending physician's discretion. Each patient's symptoms were quantified by the Geneva score.[1] The Geneva score takes into account 8 variables (recent surgery, previous thromboembolic event, older age, hypocapnia, hypoxemia, tachycardia, band atelectasis, and elevation of a hemidiaphragm on chest x-ray film) and assigns a score. The score then stratifies patients into low (≤ 4), intermediate (5-8), and high

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risk for PE (≥ 9). PE was diagnosed if either the CTA or US were positive. It was ruled out if both were negative and there was no clinical recurrence during 3 months of follow up.

Fourteen patients were excluded from the study, leaving 197 for analysis. They were predominantly male (84%) and middle-aged (average, 60.5 years). Most (69%) were referred from the emergency department; the rest were inpatients who had an acute COPD exacerbation during hospitalization. Based on the ATS severity criteria, 41% were grade I, 42% grade II, and 17% grade III. One-quarter were on long-term oxygen. Fifty-seven patients (29%) had a cancer diagnosis (lung, breast, colon, head and neck, gastric, and prostate accounted for 93%). Forty-nine patients (25%) had PE.

On bivariate analysis, only a decrease in $PaCO_2$ of at least 5 mm Hg from baseline, history of thromboembolic disease, and a cancer diagnosis were associated with PE. Dyspnea, pleuritic pain, hemoptysis, tachycardia, lower extremity edema, the need for long-term oxygen therapy, the level of hypoxemia on admission, the level of hypocapnia on admission, and recent trauma or surgery were not associated with PE.

When the patients were stratified by Geneva score, 119 (60%) were low-risk, 75 (38%) were intermediate risk, and 3 (1.5%) were high risk. PE was confirmed in 11 (9%), 35 (47%), and 3 (100%), respectively. The authors modified the Geneva score by substituting "associated underlying malignant disease" for "recent surgery" and recalculated the scores. Under the modified score, 93 patients (47%) were low risk, 88 (45%) intermediate risk, and 16 (8%) high risk. PE was confirmed in 3 (3%), 34 (39%), and 12 (75%), respectively.

## COMMENTARY

The *raison d'etre* of clinical decision tools, such as the Geneva score, is to identify patients at low risk for a particular condition and who do not need any further diagnostic testing ("sensitivity") from those who are at high risk and do ("specificity"). A good rule of thumb is a highly specific test (> 95%) when positive rules in disease, and a highly sensitive test (> 95%) when negative rules out disease. In this study the original Geneva score identified 119 low-risk patients, 11 who had PE, and 108 who didn't. If we combine the intermediate- and high-risk groups, 38 patients out of 78 had PE, and 40 didn't. This yields a sensitivity of 78% (38/38 + 11), a specificity of 73% (108/108 + 40), a positive predictive value (PPV) of 49% (38/38 + 40), and a negative predictive value (NPV) of 9% (11/11 + 108). Not good enough to rule in or rule out PE. Applying the same analysis to the modified Geneva score, the sensitivity is 94% (46/46 + 3), the specificity is 87% (90/90 + 58), the PPV is 44% (46/46 + 58), and the NPV is 3% (3/3 + 90). Better, especially the sensitivity, but still not ready for prime time. Now remember that this study was performed on a highly select population. It's reasonable to infer that patients coming to a Lung Department might not have garden-variety COPD, and the large percentage of patients with a coexisting malignancy signals that this population is not one seen in primary care offices. The prevalence of PE (25%) was high. PPV and NPV are sensitive to the prevalence of the disease in the population. In a population with a lower prevalence (our folks) the PPV will fall and the NPV will rise. (If your eyes are glazing over with this inundation of statistics, I suggest you read Loong's terrific article in *BMJ*.[2]) The take-away message here is that you *might* consider PE in your COPD patients with unexplained exacerbations and proceed

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with additional testing. This study did not use D-dimer to diagnose PE. You might want to include it in your evaluation. A recent randomized trial[3] concluded that PE occurs very infrequently (< 1%) in low-risk patients with negative D-dimer results and that additional diagnostic testing can be withheld. ■


**References**

1. Wicki J, et al. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med*. 2001;161:92-97.
2. Loong TW. Understanding sensitivity and specificity with the right side of the brain. *BMJ*. 2003;327: 716-719.
3. Kearon C, et al. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. *Ann Intern Med*. 2006;144:812-821.


# Does an MRI Diagnose Multiple Sclerosis?

ABSTRACT & COMMENTARY


***By Joseph E. Scherger, MD, MPH***

*Clinical Professor, University of California, San Diego*

*Dr. Scherger reports no financial relationships to this field of study.*



***Synopsis:*** *An MRI is often used to assist in the diagnosis of multiple sclerosis. This systematic review of 29 studies shows that an MRI will result in an overdiagnosis of MS when used after one episode of neurologic dysfunction. A negative MRI may contribute to an underdiagnosis of MS. While the MRI may be useful in the diagnosis of MS, the study lacks the specificity and sensitivity to be relied on as a primary diagnostic tool.*


**Source:** Whiting P, et al. Accuracy of magnetic resonance imaging for the diagnosis of multiple sclerosis: systematic review. *BMJ*. 2006;332:875-884.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system characterized by multifocal areas of demyelination and variable degrees of axonal loss and gliosis resulting in neurologic dysfunction. This definition based on neuropathologic evidence is not practical clinically since biopsy of the central nervous system is not feasible. Hence, the diagnosis is made clinically based on recurrent episodes of neurologic dysfunction such as optic neuritis, transverse myelitis, double vision, or numbness or tingling of the leg. Many years may elapse between first and second episodes, and not all patients who experience a first attack develop multiple sclerosis.

Magnetic resonance imaging (MRI) may assist in earlier diagnosis of MS by visualization of white matter lesions suggesting demyelination in the brain or spinal cord that are clinically silent. In 2001, an international panel on the diagnosis of multiple sclerosis published diagnostic criteria which allows for an early diagnosis of MS after one clinical attack if the patient also meets criteria for a positive result on an MRI.[1] These are referred to as the McDonald criteria and have resulted in earlier diagnosis of MS worldwide, both to the benefit and detriment of patients.

Patients may benefit from early diagnosis by receiving early disease limiting treatment, such as interferon beta-1α. It remains controversial whether the ultimate course of the disease can be modified by early treatment due to a lack of long-term studies of more than 10 years. Patients may be harmed from early diagnosis if they do not ultimately have MS, and receive both the negative psychological consequences of being labeled with the disease and an inability to get life and health insurance.

This systematic review concludes that the accuracy of MRI for the early diagnosis of MS has inflated estimates of test performance based on studies with methodological weaknesses. The use of MRI to confirm multiple sclerosis on the basis of a single attack of neurological dysfunction may lead to overdiagnosis and overtreatment.

## ■ COMMENTARY

Over the past 10 years I have noticed an increasing number of patients reporting a diagnosis of MS. Some have no apparent neurologic dysfunction. They report a past episode of weakness of some type and that an MRI confirmed the diagnosis of MS. Such a diagnosis has a profound impact on a patient's sense of well-being and potential in life!

To get an idea of the passion and controversy in the criteria for diagnosing MS, look at the responses to this article in the *BMJ* (available through Pub Med and bmj.com). Many clinicians are wedded to the early diagnosis of MS, and strongly believe that early therapy may prevent the development and progression of the disease. This is fine if the patient actually has MS. Receiving interferon therapy is not a matter to be taken lightly.

The systematic review by Whiting et al gives some idea of the natural history of transient neurologic dysfunction. In one study of optic neuritis, a common presenting symptom of MS, only 38% of patients developed the disease by 10 years.[2] Other clinically isolated symptoms of the brain and spinal cord showed that 68%

developed MS by 14 years.[3] In patients with mild and transient findings, a wait and see approach is still taken by the wise clinician.

This systematic review of the use of MRI in the diagnosis of MS, the first of its kind, reminds us that advanced imaging does not make a definitive diagnosis. Only tissue can do that. While this is not practical for MS, and the diagnosis must be made clinically, we must avoid an over reliance on MRI and avoid the mislabeling of patients with this very serious disease. ■

### References


1. McDonald WI, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel of the diagnosis of multiple sclerosis. *Ann Neurol*. 2001;50:121-127.
2. Beck RW, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Arch Ophthalmol*. 2003;121:944-949.
3. Brex PA, et al. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med*. 2002;346:158-164.


# Which Non-Invasive Test is Best for the Diagnosis of Clinically Significant Carotid Artery Stenosis?

ABSTRACT & COMMENTARY


***By Matthew E. Fink, MD***

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*Dr. Fink reports no financial relationship relevant to this field of study.*



***Synopsis:*** *All of the currently available non-invasive techniques for carotid artery imaging give accurate results when there is a high-grade stenosis (70-99%), but contrast-enhanced MRA is slightly more sensitive.*



**Source:** Wardlaw JM, et al. Non-Invasive Imaging Compared with Intra-Arterial Angiography in the Diagnosis of Symptomatic Carotid Stenosis: A Meta-Analysis. *Lancet*. 2006;367:1503-1512.


With improvements in the treatment of extracranial carotid artery stenosis using carotid endarterectomy (CEA) and carotid artery stenting (CAS), it has become important for clinicians to understand the relative accuracy of various non-invasive tests for carotid stenosis that can be used as a screening procedure or as a definitive study prior to referral for treatment. There have been few head-to-head studies that have directly compared Doppler ultrasound (DUS) with MR angiography (MRA), with and without contrast enhancement (CEMRA), and CT angiography (CTA). Therefore, Wardlaw and colleagues performed a meta-analysis of all studies in the English language literature from 1980-2004 that evaluated the sensitivity and specificity of various non-invasive carotid studies compared to either NASCET or ECST criteria for angiography. To be included in the analysis, the published studies had to meet the Standards for Reporting of Diagnostic Accuracy, as well as the methods of the Cochrane Database of Systematic Reviews. After excluding all papers from 1980-1986 because of obsolete technology, and eliminating those papers that did not define what proportion of patients or arteries were symptomatic, there were 41 original papers available for inclusion. For each paper, the authors computed an estimate for sensitivity and specificity with 95% confidence intervals (CIs) for each non-invasive imaging technique compared with intra-arterial angiography.

In the 41 studies, which represented 2541 patients and 4876 arteries, contrast-enhanced MR angiography was more sensitive (0.94, 95% CI = 0.88-0.97) and specific (0.93; 95% CI = 0.89-0.96) for 70%-99% stenosis than Doppler ultrasound, MR angiography without contrast, or CT angiography (sensitivities = 0.89, 0.88, 0.76; specificities 0.84, 0.84, 0.94, respectively). For any degree of stenosis less than 70%, none of the non-invasive tests were deemed reliable when compared to intra-arterial angiography, and data regarding any combination of tests were too sparse to draw any conclusions.

## ■ COMMENTARY

Non-invasive testing for carotid artery disease is widely available and liberally utilized as part of the clinical identification of stroke risk factors. In symptomatic patients who have had a TIA or stroke, where treatment decisions are urgent, we often combine tests, commonly DUS with MRA, or DUS with CTA, prior to CEA or CAS. The study by Wardlaw et al seems to indicate that all of the available, non-invasive tests are reasonably sensitive and specific when the degree of stenosis is 70%-99% and, probably, it is not necessary to proceed with intra-arterial angiography before surgery or stenting if a high-grade stenosis is found. CEMRA is slightly more sensitive than the other tests, and CTA is slightly

more specific. In those patients who are symptomatic with lesser degrees of stenosis (ie, 50%-69%), the sensitivity and specificity of the non-invasive studies is not very high, but there is a lack of good data to compare the various studies. Because the indications for surgical or endovascular therapy in this group with less than 70% stenosis is not as clear and the therapeutic benefit is small, we would continue to recommend intra-arterial angiography if CEA or CAS is being considered. In addition, we need to continue to collect data in a prospective and blinded fashion in the moderate stenosis group and compare the results with intra-arterial angiography whenever possible. As morbidity and mortality from CEA and CAS continues to improve, there will be a desire to treat more patients with moderate stenosis, and more accurate non-invasive carotid imaging would be helpful. ■

*Pharmacology Update*

# Varenicline Tartrate Tablets (Chantix™)

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

*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 relationships to this field of study.*

THE FDA HAS APPROVED A NEW AGENT FOR SMOKING cessation. Varenicline is a partial agonist of the α4β2 subtype of nicotinic receptors. It blocks the action of nicotine but provides a lower level of stimulation of dopamine release to reduce craving and withdrawal symptoms. Chemically and pharmacologically, varenicline is similar to cytosine, a plant alkaloid used in Eastern Europe. It is marketed by Pfizer Labs as Chantix™.

## Indications

Varenicline is indicated as an aid to smoking cessation treatment.[1]

## Dosage

The recommended dose is 1 mg twice daily with a full glass of water after eating. This should be titrated from 0.5 mg once daily for 3 days, 0.5 mg twice daily for 4 days, then 1 mg twice daily thereafter. Treatment should start one week before the 'stop smoking date' and continue for 12 weeks. For those who have successfully stopped smoking at the end of the period, an additional 12 weeks of treatment is recommended. For patients with severe renal impairment, the recommended dose is 0.5 mg twice daily and for those with end-stage renal disease on hemodialysis, a maximum dose of 0.5 mg daily is recommended.[1]

Varenicline is supplied as 0.5 mg and 1 mg tablets.

## Potential Advantages

Varenicline appears to be more effective than bupropion.[1-3] No drug-drug interaction has been demonstrated.

## Potential Disadvantages

Nausea and insomnia are the most common side effects. Nausea is generally mild or moderate in severity and usually transient. However it may persist in some patients. Abrupt discontinuation of varenicline results in irritability and/or sleep disturbance in 3% of patients.[1]

## Comments

Nicotine activates the α4β2 subtype of nicotinic receptors in the brain resulting in dopamine release. Repeated exposure to nicotine and dopamine response is believed to be associated with reinforcement and addictive properties of nicotine.[2] Varenicline acts as a partial agonist thus blocking the nicotine receptor to nicotine but providing moderate levels of dopamine release to reduce withdrawal and craving. Efficacy was shown in 6 clinical trials. Typical subjects used an average of 21 cigarettes per day for an average of 25 years. Abstinence was self-reported and verified by exhaled carbon monoxide measurements. In patients randomized to 1 mg twice daily, continuous abstinence rates (weeks 9-52) were 23% compared to 4% for placebo. In two comparative trials (n = 1022,1023), continuous abstinence was 21%-22% for varenicline, 14-16% for bupropion SR (150 mg twice daily), and 8-10% for placebo. An additional 12 weeks of treatment in subjects who had successfully quit smoking at week 12 resulted in 54% with continuous abstinence at week 52 (40 weeks post treatment) compared to 39% with only 12 weeks of treatment. Varenicline appears to be well tolerated with nausea (30%) the most common adverse event. Discontinuation of treatment during placebo-controlled trials was 12% for varenicline compared to 10% for placebo. The wholesale cost for varenicline is $269 for a 12-week course.

## Clinical Implications

Smoking is implicated in increases risks of several types of cancer and chronic diseases. The CDC estimates that there are 44.5 million smokers in the United

States and 8.6% have chronic disease directly related to smoking. Approximately 50% of long-term smokers die prematurely from the effects of smoking.[4] Most smokers are addicted to nicotine and have difficulty quitting. There are currently several available effective pharmacotherapies for smoking cessation.[5] These include nicotine replacement, bupropion, nortriptyline, and clonidine. Abstinence rates have been generally disappointing, ranging from 15-25% at 6-12 months compared to 9-12% for placebo.[2] Varenicline provides a drug with a different mechanism of action and may be marginally better than bupropion. ■

### References


1. Chantix Product Information. Pfizer Labs. May 2006.
2. Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. *Int J Clin Pract*. 2006;60:571-576.
3. Fagerstrom K, Balfour DJK. Neuropharmacology and potential efficacy of new treatments for tobacco dependence. *Expert Opin Investig Drugs*. 2006;15:107-116.
4. Henningfield JB, et al. Pharmacotherapy for nicotine dependence. *CA Cancer J Clin*. 2005;55:281-299.
5. Foulds J, et al. Developments in pharmacotherapy for tobacco dependence: past, present and future. *Drug Alcohol Rev*. 2006;25:59-71.


## CME Questions

1. **Which statement best reflects the role of MRI in the diagnosis of multiple sclerosis (MS)?**
   a. MRI is used to confirm the diagnosis of MS after a classic episode of neurologic dysfunction such as optic neuritis.
   b. MRI is highly specific in demonstrating the pathologic lesions of MS and may give clinicians the diagnosis of MS in asymptomatic patients.
   c. When a patient gets two or more transient episodes of neurologic dysfunction, a positive MRI establishes the diagnosis of MS.
   d. While MRI findings may suggest the diagnosis of MS, the lesions seen in the white matter are not definitively diagnostic.

2. **Choose the correct answer. In the study of patients with unexplained exacerbation of chronic obstructive pulmonary disease, those with pulmonary embolism were more likely to have:**
   a. a cancer diagnosis.
   b. pleuritic pain.
   c. hemoptysis.
   d. tachycardia.
   e. dyspnea.

**Answers:** 1 (d); 2 (a)

## 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; and
- to describe cost-effective treatment regimens.



## Readers are Invited. . .

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*By Louis Kuritzky, MD,* *Clinical Assistant Professor, University of Florida, Gainesville*
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## Effect of Lowering LDL Cholesterol Substantially Below Currently Recommended Levels in Patients with Coronary Heart Disease and Diabetes: the Treating to New Targets (TNT) Study

The TNT study (treat to new targets) demonstrated that intensive lipid lowering (ILL) with atorvastatin 80 mg/d in patients with stable coronary artery disease (CAD) provided more benefit than simply achieving an LDL of 100 mg/dL with atorvastatin 10 mg/d. This trial provided useful information because it came on the heels of the PROVE-IT trial, which had demonstrated that for persons with acute coronary syndromes, ILL provided greater risk reduction than modest LDL lowering. Whether patients with diabetes in the TNT trial enjoyed similar benefits from ILL had not been previously reported.

There were 1,501 diabetics in TNT. Those on atorvastatin 10 mg achieved a mean LDL of 98.6 mg/dL, compared to an LDL of 77.0 mg/dL for subjects on atorvastatin 80 mg. The lower LDL level was associated with a 25% relative risk reduction for a new primary event, defined as death from coronary heart disease, non-fatal MI, or stroke (103 events vs 135 events). Although all-cause mortality was slightly higher in subjects who received ILL, the difference was not statistically significant. Higher dose atorvastatin was not associated with any safety concerns. ■

*Shepherd J, et al. Diabetes Care 2006;29:1220-1226.*

## Colonoscopy in Very Elderly Patients: Prevalence of Neoplasia and Estimated Impact on Life Expectancy

In contrast to guidance available for clinicians in reference to cessation of screening tools like PAP tests, where there is age-specific direction offered, the current guidelines on screening colonoscopy (sCOL) do not provide any age limit. Colon cancer incidence increases with age, so the yield of screening older persons would be anticipated to be greater than younger individuals. However, at advanced age life expectancy decreases, such that quantifying potential benefits must take age into account.

Lin et al, performed a cross-sectional study (n = 1,244) of sCOL in three groups divided by age: 50-54 years, 75-79 years, and > 80 years. Outcomes of the study included colonic neoplasia detected and gain in life expectancy, with comparisons between age groups.

There was a linear relationship between age and prevalence of neoplasia: 13.8% (age 50-54), 26.5% (age 75-79), and 28.6% (age > 80). Nonetheless, mean gain in life expectancy was substantially lower (6.5-fold lower!)in the oldest age group than the youngest.

Even though sCOL did provide gains in life expectancy, the results were markedly less substantial in the most aged seniors. These data do not provide evidence for any age limit to appropriate use of sCOL. Rather, they may assist in weighing the risk-benefit ratio for sCOL in older persons, depending upon their anticipated life expectancy, individual health issues, and personal preferences. ■

*Lin O, et al. JAMA. 2006;295: 2357-2365.*

## Is There an Iraq War Syndrome? Comparison of the Health of UK Service Personnel after the Gulf and Iraq Wars

The so-called Gulf War syndrome (GWS) is an ill-defined umbrella term to describe the non-specific health complaints registered by armed forces personnel who served in this conflict. Subsequent to the 1991 Gulf War, data from the United States, United Kingdom, Canada, Denmark, and Australia corroborated increases in symptomatic disease, although no clearly-defined syndromic definition evolved. Indeed, it has been opined that the symptoms attributed to the Gulf War may simply be consistent with other issues such as emotional stress and new vaccinations.

Subsequent to the Gulf War, the UK Ministry of Defense funded a project to provide detailed surveillance of health issues for personnel serving in Iraq post the 2003 invasion. In addition to a checklist of the same 50 non-specific symptoms used in GWS screening, they also assessed fatigue (with a validated 13-item scale) and general health (with an item from the SF-36).

In contrast to personnel from the Gulf War, UK personnel in Iraq did not demonstrate any evidence of health effects. It is reassuring to note that heightened surveillance does not detect an "Iraq syndrome." ■

*Horn O, et al. Lancet. 2006;367: 1742-1746*

# RBBB with a Twist

***By Ken Grauer, MD,*** *Professor, Assistant Director, Family Practice Program, University of Florida*
*Dr. Grauer reports no financial relationship to this field of study.*

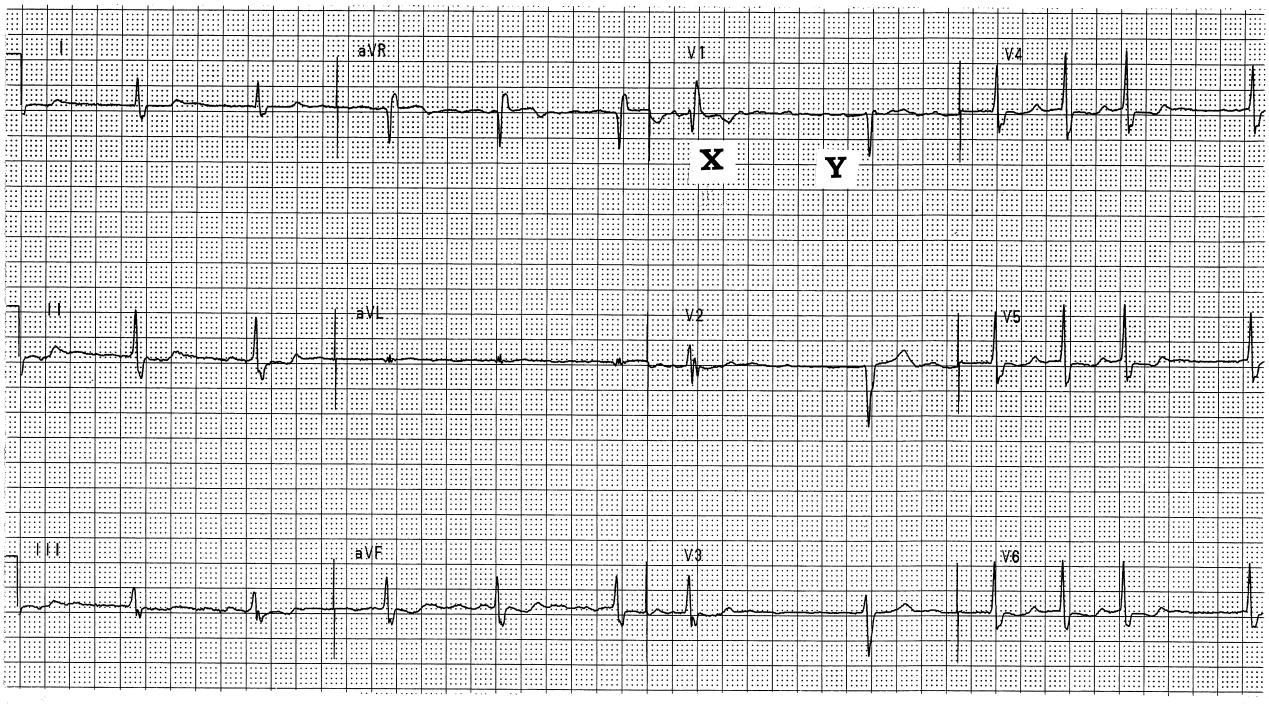


**Figure.** 12-lead ECG obtained from a 66 year old man with heart failure.

**Clinical Scenario:** The 12-lead ECG in the Figure was obtained from a 66 year old man with heart failure. How would you interpret this ECG? Does the patient have RBBB (right bundle branch block)? Is there "a twist" to answering this question?

**Interpretation/Answer:** Although we are not provided with a lead II rhythm strip, the rhythm is clearly irregular. There are undulations in the baseline, but no definite P waves. Given the irregular irregularity and lack of P waves, the rhythm is atrial fibrillation, in this case with a relatively slow ventricular response.

The QRS complex appears to be widened (to about 0.11 second) in most leads. The typical rSR' morphology of the beat labeled X in lead $V_1$, in association with QRS widening and wide terminal S waves in leads I and $V_6$ is consistent with the diagnosis of complete RBBB (right bundle branch block).

The most interesting facet of this tracing is beat Y in lead $V_1$. This QRS complex is not widened! Instead, QRS morphology of this complex in simultaneously recorded leads $V_1$, $V_2$, $V_3$ is completely normal. This suggests that the RBBB conduction defect is not permanent. Instead, it is likely to be rate-related, with the relative pause seen between beats X and Y being long enough to allow the defective right bundle branch adequate time to recover its conduction capacity.

Rate-related bundle branch block is an interesting phenomenon that will be seen on occasion. The rate of onset of the conduction defect often differs from the rate at which the conduction defect goes away. Thus, a patient may manifest normal QRS conduction at a rate up to 80/minute, beyond which RBBB may develop. However, the heart rate may then need to slow down to well *under* 50 or 60/minute before the conduction defect goes away. Cardiac ischemia or hypoxia may both contribute to development of an intermittent or rate-related conduction defect. The diffuse ST-T wave flattening and slight depression seen in the tracing shown here may have reflected ischemia in this 66-year-old man with heart failure. ■

## In Future Issues:

**Itopride in Functional Dyspepsia**

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.

# Capping Drug Benefits—Will it Help Control Healthcare Costs?

Controlling healthcare costs is tricky business, and sometimes the best intentions have adverse outcomes, as pointed out in a new study in the June 1 *New England Journal of Medicine*. Financial caps on Medicare drug benefits were reviewed in a large group of Medicare + Choice beneficiaries in northern California (over 150,000 individuals) who had $1,000 annual drug benefit cap compared to those who did not have a limit on their drug benefits (41,904 individuals). The cap on pharmacy costs was effective at reducing pharmacy costs by 31% (95% CI, 29 to 33%), but the capped group had total healthcare costs that were only 1% lower overall (95% CI, -4 to 6%). Those with capped benefit were more likely to visit the emergency department (RR, 1.09 [1.04 to 1.14) and were also more likely to be hospitalized for non-elective admissions (RR, 1.13 [1.05 to 1.21]). The death rate was also higher in the capped group (RR, 1.22), with a difference of 0.68 per hundred person-years [0 .30 to 1.07]. Patients on chronic medications for hypertension, hyperlipidemia, or diabetes were more likely to be nonadherent to drug therapy if they had a capped benefit and, for each of those diagnoses, physiologic outcomes were worse for subjects with capped drug benefits, including systolic blood pressure over 140 mm Hg, serum LDL greater than 130, and a HbgA1c over 8 (respective risk ratios 1.05 [1.00 to 1.09], 1.13 [1.03 to 1.25], 1.23 [1.03 to 1.46]).

The authors conclude that a cap on drug benefits was associated with lower drug consumption and unfavorable clinical outcomes. In patients with chronic diseases, the benefit cap was associated with nonadherence to drug therapy and poorer clinical outcomes. Overall, any savings realized by a drug cap was offset by an increase in the rate of hospital admissions and emergency department visits (*N Engl J Med*. 2006;354:2349-2359). An accompanying editorial states, "Effective strategies for reducing the level and growth of spending will need to rely on tools other than high-deductible plans and limits on benefits" such as preventative care and dealing with the obesity epidemic, as well as improved information systems (*N Engl J Med*. 2006;354:2385-2386).

### *The STAR Trial (Tamoxifen and Raloxifene)*

Results from the long awaited STAR trial (the National Surgical Adjuvant Breast and Bowel project Study of Tamoxifen and Raloxifene) have been published as an early release article on the *JAMA* website. This multicenter trial of nearly 20,000 women mean age 58.5 years with an increased 5-year breast cancer risk was designed to compare the incidence of invasive breast cancer, uterine cancer, noninvasive breast cancer, bone fractures, and thromboembolic events in those treated with oral tamoxifen 20 mg per day or raloxifene 60 mg per day over 5 years. Tamoxifen has been used to treat early and advanced breast cancer for more than 30 years, and has also been shown to reduce the risk of invasive and non-invasive breast cancer in women who were at increase risk.

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The STAR was designed to see if the second-generation selective estrogen receptor modulator (SERM) raloxifene would also be effective in this role. Raloxifene is currently approved for the prevention and treatment of postmenopausal osteoporosis. After 5 years, there were 163 cases of invasive breast cancer in the tamoxifen group and 168 in the raloxifene group (incidence, 4.30/1000 vs 4.41/1000; RR, 1.02; 95% CI, 0.82 to 1.28). Noninvasive breast cancers were slightly more common in the raloxifene group (1.52 vs 2.11 cases per 1000; RR, 1.40; 95% CI, 0.98 to 2.00). The rate of uterine cancer was lower in the raloxifene group (RR, 0.62; 95% CI, 0.35 to 1.08). No differences were found for other invasive cancers, ischemic heart disease, stroke, or osteoporotic fractures. Thromboembolic events were more common in the tamoxifen group (RR, 0.70 nickel and 95% CI, 0.54 to 0.91). Cataracts and cataract surgery were also less common in the raloxifene group. The overall death rate and the causes of death were the same in both groups.

The authors conclude that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer, and has a lower risk of thromboembolic events and cataracts but is associated with a nonsignificant higher risk of noninvasive breast cancer (*JAMA* early release, posted online June 5, 2006 jama.ama-assn.org). This study is important because although there was no control group, tamoxifen is proven to reduce breast cancer incidence and is approved for this indication, but with a higher incidence of endometrial cancer, thromboembolic events, DVT, and stroke. Previous studies have shown that raloxifene reduces the risk of estrogen receptor-positive invasive breast cancer by up to 66% over 8 years of treatment compared to placebo (MORE and CORE trials [*JNCI* 2004;96:1751-1761]). Quality-of-life issues have been a concern with SERMs, and was hoped that raloxifene would be the better tolerated than tamoxifen.

An accompanying article also published online focused on patient reported symptoms and quality of life issues in participants in the STAR trial. There was no significant differences between tamoxifen and raloxifene in patient reported outcomes for physical health, mental health, and depression, although the tamoxifen group reported better sexual function (age-adjusted repeated measure odds ratio 1.22%; 95% CI, 1.01 to 1.46). Women in the raloxifene group reported more musculoskeletal problems ($P = .002$), dyspareunia ($P < .001$), and weight gain ($P < .001$). Women in the tamoxifen group reported greater severity of gynecological problems ($P < .001$), vasomotor symptoms ($P < .001$), leg cramps ($P < .001$), and bladder control symptoms ($P < .001$). Overall, mean symptom severity was low among women in both groups (*JAMA*. early release, posted online June 5, 2006 jama.ama-assn.org).

An accompanying editorial points out that tamoxifen is rarely used as an agent for protection against breast cancer in women at risk, and it had been hoped that raloxifene would provide an alternative with equal efficacy for breast cancer and less adverse effects. Unfortunately, the STAR trial does not clearly demonstrate this. Both drugs are effective at preventing breast cancer but both carry increased risk of endometrial cancer and thromboembolic events. Raloxifene has an advantage of being approved for reduction of osteoporotic fractures, but whether this will convince primary care physicians to prescribe the drug for women at risk of breast cancer is unknown (*JAMA*. early release, posted online June 5, 2006 jama.ama-assn.org).

## FDA Actions

Merck has received approval to market a vaccine to prevent human papilloma virus (HPV) infections. The vaccine received a priority review, and is seen as a major advance because of the association between HPV and cervical cancer. The vaccine targets HPV types 16 and 18, which are responsible for 70% of cervical cancers and types 6 and 11, which are the most common cause of genital warts. HPV vaccine is given in 3 separate IM injections over 6 months and will cost $120 per dose, $360 for the entire course. It is approved for use in females age 9 to 26. Merck will market the HPV vaccine as Gardisil.

Merck has also received approval to market its live zoster vaccine for the prevention of herpes zoster in individuals aged 60 and older. The vaccine, which is a live attenuated varicella-zoster virus, is given as a single-dose subcutaneous injection. The vaccine has been shown to significantly decrease the rate of varicella-zoster (shingles) in older adults and decrease the rate of postherpetic neuralgia in those who developed shingles despite the vaccine. Merck will market the live zoster vaccine as Zostavax. ■