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## INSIDE



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# (Doctor) Shop Till You Drop

ABSTRACT & COMMENTARY

***By Barbara A. Phillips, MD, MSPH***

*Professor of Medicine, University of Kentucky;*
*Director, Sleep Disorders Center, Samaritan Hospital, Lexington*

*Dr. Phillips reports no relationship to this field of study.*

***Synopsis:*** *Most deaths due to overdose in West Virginia involved men who took opioids that were not prescribed for them.*

**Source:** Hall AJ, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA* 2008;300:2613-2620.

WEST VIRGINIA HAD THE HIGHEST INCREASE IN ACCIDENTAL overdose during the 5-year period between 1999 and 2004. The authors of this study, who are from the Centers for Disease Control and Prevention, the West Virginia Board of Pharmacy, the West Virginia Health Statistics Center, the West Virginia Office of the Chief Medical Examiner, and the Charleston WV Area Medical Center, wanted to find out why.

Using death certificates coded for unintentional poisoning, they identified 355 unintentional pharmaceutical overdose deaths between 1999 and 2004. After excluding duplicate reports, those with coding errors, and those which lacked autopsy or adequate toxicology, they had a study sample of 295 well-documented, well-described drug overdose cases. In West Virginia, the Office of the Chief Medical Examiner extensively reviews deaths that are suspected of being due to drug overdose, including board of pharmacy records, medical records, police investigative reports, and toxicology reports; each case receives final peer review to determine which factors, including drugs, are contributory to death. In addition, the authors obtained histories from the state's Controlled Substances Monitoring Program and all 8 opiate treatment programs in West Virginia. In those individuals for whom prescription pharmaceuticals were found as part of the cause of death, the authors investigated whether they had ever had a documented prescription for the pharmaceutical.

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These authors particularly evaluated 2 mechanisms by which those who overdosed got drugs: drug diversion and doctor shopping. Drug diversion was defined as prescription drug used without documented prescription records. The clear implication here is that the patient got the drug from someone else. Doctor shopping was defined as having received prescriptions for controlled substances from 5 or more clinicians during the year prior to death. They also classified deaths by the specific causal drugs. For each drug, they calculated the proportion of deaths with prescription documentation as well as the proportion with documentation within 30 days of death. They also calculated the proportion of overdose victims that were using each drug who also were using other contributory prescription drugs, illicit drugs, or alcohol.

The 295 well-documented and described cases accounted for a death rate of 16.2 per 100,000. Men accounted for 67% of the deaths, and the mean age was 39 years. A majority of those who died were 18-54 years of age. Lower socioeconomic status and being single were also associated with an increased risk of fatal overdose.

Of those who died of drug overdose, 63% obtained the drugs without a prescription (drug diversion) and 21% had been doctor shopping. Women and older individuals were more likely to be doctor shoppers. Those who obtained drugs by diversion were younger; 91% of those aged 18-24 did not have documentation of a prescription for the drug. Notably, few (about 8%) individuals engaged both in doctor shopping and in drug diversion.

At least one substance abuse indicator (defined as history of substance abuse, any diverted pharmaceuticals, nonmedical route of administration, ≥ 5 physicians prescribing controlled substances, contributory alcohol, previous overdose, contributory illicit drug use, or current opiate treatment program) was seen in virtually all (94.6%) of those who died from drug overdose. Further, most (about 79%) of those who died of drug overdose had used multiple substances contributing to their death. The vast majority (93%) of drugs involved in these fatal overdoses were opioids, including methadone (40%), hydrocodone (22.7%), oxycodone (20.7%), morphine (15.6%), and fentanyl (10.5%). Of the 227 individuals for whom Schedule II opioid analgesics contributed to death, only 66 (29.1%) had prescriptions dispensed within 30 days prior to death, as is the law in West Virginia.

Psychotherapeutic drugs, particularly benzodiazepines, contributed to almost half of the deaths, but almost all of the deaths related to psychotherapeutic drugs also involved opioids. In other words, among the 61 single-drug deaths, only 1 was due to a psychotherapeutic drug (amitriptyline), suggesting that fatal overdose is less likely with a single psychotherapeutic drug than with a single opioid analgesic. Alcohol was involved in fewer than 20% of cases.

## ■ COMMENTARY

Two expert panels introduced guidelines for chronic pain management in 1997,[1,2] and state medical boards subsequently have encouraged more compassionate pain policies.[3] Since that time there has been an explosive increase in per capita retail purchases of methadone (13-fold), hydrocodone (4-fold), and oxycodone (9-fold).[4] Unfortunately, as opioids have become more widely available, abuse of these agents has also increased. Some of the unintended consequences of this change in prescribing practice have been increased experimentation by children,[5] increased emergency department visits for opioid overdose,[6] and increased fatal drug overdose.[7] Although West Virginia is among the states with the highest rates of opioid use and abuse, it is by no means unique.

What can we learn from the detailed study of drug overdose in West Virginia? Drug diversion was the most common method of obtaining the drugs that killed the patients in this report. An analysis of drug diversion in Appalachia by the Drug Enforcement Agency discovered that the primary methods of diversion were illegal sale and distribution by health care professionals, employee theft, forged prescriptions, and the Internet.[8]

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Please call **Paula Cousins**, Senior Managing Editor, at (404) 262-5468

So, one lesson here is to control your prescription pads carefully, and to pay attention to workers in your area.

Another practical finding of this study was the profile of the doctor shopper. In this study, doctor shoppers were 48% women, and most were older than age 35. They tended to come from higher-income counties, to be less likely to have been drinking when they overdosed, and to take their drugs orally. So, beware of the older woman who is seeing several physicians and who has chronic pain. In this study, methadone, which is prescribed in smaller volumes than other opioids, was involved in more deaths than any other agent. The authors concluded, "This suggests either that methadone is for unknown reasons favored by drug diverters or that methadone is more risky to users than other opioids."

What else can we do? The authors of this study made several other practical suggestions, including counseling patients who receive opioids about the risk to themselves and others; following recently published guidelines; and using state prescription drug monitoring programs to determine whether patents are getting scheduled drugs from other clinicians. ■

**References**


1. Practice guidelines for chronic pain management. A report by the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. *Anesthesiology* 1997;86:995-1004.
2. The use of opioids for the treatment of chronic pain: A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain* 1997;13:6-8.
3. Model Policy for the Use of Controlled Substances for the Treatment of Pain. Federation of State Medical Boards of the United States Inc. Available at: www.fsmb.org/pdf/2004_grpol_Controlled_Substances.pdf. Accessed Dec. 16, 2008.
4. ARCOS: Automation of Reports and Consolidated Orders System. U.S. Department of Justice, Drug Enforcement Administration. Available at: www.deadiversion.usdoj.gov/arcos/index.html. Accessed Dec. 16, 2008.
5. The National Survey on Drug Use and Health Report: Patterns and Trends in Nonmedical Prescription Pain Reliever Use: 2002 to 2005. Substance Abuse and Mental Health Services Administration. Available at: www.oas.samhsa.gov/2k7/pain/pain.pdf. Accessed Dec. 16, 2008.
6. Drug Abuse Warning Network, 2005: National Estimates of Drug-related Emergency Department Visits. Substance Abuse and Mental Health Services Administration. Available at: http://dawninfo.samhsa.gov/files/DAWN-ED-2005-Web.pdf. Accessed Dec. 16, 2008.
7. Centers for Disease Control and Prevention. Unintentional poisoning deaths—United States, 1999-2004. *MMWR Morb Mortal Wkly Rep* 2007;56:93-96.
8. National Drug Intelligence Center. Drug Market Analysis 2008: Appalachia High Intensity Drug Trafficking Area. Washington, DC: U.S. Dept of Justice; 2008. Report 2008-R0813-001.


# Early Stage Prostate Cancer Unlikely to Affect Survival

ABSTRACT & COMMENTARY


***By Mary Elina Ferris, MD***

*Clinical Associate Professor, University of Southern California*

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



***Synopsis:*** *Older men with early stage prostate cancer had survival similar to those without cancer; for two-thirds of these men, cardiovascular diseases and other cancers were more likely to cause death than prostate cancer.*



**Source:** Ketchandji M, et al. Cause of death in older men after diagnosis of prostate cancer. *J Am Geriatr Soc* 2008 Nov 18; Epub ahead of print.


USING A POPULATION-BASED CANCER REGISTRY (SEER) matched with Medicare data, 99,388 men aged 66-84 diagnosed with prostate cancer between 1992 and 2002 were compared to age-matched non-cancer controls. Early stage cancers were identified in 81% with clinical Stage T1 or T2 tumors, and 72% with low- to moderate-grade tumors.

Comparison of survival curves for ages 65-74 with Stage T1 or T2 tumors closely resembled the survival of patients without cancer for the first 7-8 years, and then became worse than the survival of men without cancer. For men aged 75-84, T1 to T3 tumors had survival rates that closely overlapped each other and the cancer-free comparison group. Only Stage T4 prostate cancers had a clear effect on survival rate for men aged 75-84.

Overall, cardiovascular disease had similar 5-year mortality (7.2%) for the cancer patients compared to mortality from prostate cancer itself (7.7%). For men with Stage T1 or T2, low- or moderate-grade tumors (59% of all cases), mortality from heart disease was 6.4% compared to 2.1% for prostate cancer, vs 3.8%

from other cancers. Even with more disseminated prostate cancer, men with low- or moderate-grade tumors (60.5% of men with Stage 3 cancer) experienced higher rates of death from cardiovascular disease (5.2%) than from prostate cancer (4.0%).

■ **COMMENTARY**

Prostate cancer is the most common form of non-skin cancer diagnosed in men, and 75% of those cases occur in men aged 65 and older. Once cancer is diagnosed, it tends to be the predominant medical concern, yet these interesting findings suggest that comorbid medical conditions are more of a survival threat. These data come after the advent of screening with prostate-specific antigen, suggesting that early detection of prostate cancers may be altering the survival curves. Furthermore, decisions about the aggressiveness of cancer treatment should consider comorbid diseases, since androgen-deprivation therapy, used to treat even early stage prostate cancer, may increase the risk of cardiovascular events and exacerbate diabetes mellitus.[1,2] Ideally the medical care of older men with prostate cancer should involve consideration of their other chronic conditions, and decisions about early stage prostate cancer treatment should be made together with the patient's primary care physician. ■

**References**


1. D'Amico AV, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol* 2007;25:2420-2425.
2. Keating NL, et al. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24:4448-4456.


# Diagnose Frailty to Help Vulnerable Elderly

ABSTRACT & COMMENTARY


***By Mary Elina Ferris, MD***

*Clinical Associate Professor, University of Southern California*

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



***Synopsis:*** *Strong evidence was found that slow gait speed, low physical activity, and weight loss are key indicators of frailty, which is associated with chronic disability, long-term nursing home stays, injurious falls, and death.*



**Source:** Rothman MD, et al. Prognostic significance of frailty criteria. *J Am Geriatr Soc* 2008;56:2211-2216.


A PROSPECTIVE COHORT STUDY FOLLOWED 754 NON-DISabled community-dwelling persons in New Haven, CT, aged 70 and older for 6-9 years to determine the prognostic value of 7 potential frailty criteria: gait speed, physical activity, weight loss, exhaustion, weakness, cognitive impairment, and depressive symptoms. Outcomes were the occurrence of chronic disability, long-term nursing home stays, injurious falls, and death. Data were collected from comprehensive home assessments every 18 months for 6 years, followed by telephone contact for a further 3 years to determine outcomes, to give at least 7.5 years of follow-up for all participants.

The study criteria came from information obtainable in most offices: Slow gait speed was defined as > 10 seconds to walk both directions as quickly as possible on a 10-foot course. Weight loss was defined as > 10 lbs in the past year, and weakness by grip strength was measured on a hand-held dynamometer and compared to established norms. Cognitive impairment was defined as a score < 24 on Folstein Mini-Mental Status Exam, and physical activity and depression were established using standardized questionnaires. Exhaustion was established for the answer "much or most of the time" to either of the following statements, "I felt that everything I did was an effort," or "I could not get going."

Results indicated that slow gait speed, low physical activity, and weight loss were most strongly associated with chronic disability, long-term nursing home stays, and death, even after adjusting for age, sex, race, education, and other chronic conditions. Low physical activity was most associated with death, and slow gait speed was the only criteria that predicted injurious falls.

■ **COMMENTARY**

Frailty is used in geriatric medicine to describe a potentially modifiable syndrome of vulnerability to functional decline, institutionalization, and falls.[1] It would be useful to identify which of our older patients are in this group and which might benefit from medical interventions to avoid these adverse outcomes, as opposed to those patients with permanent disabilities that are best treated with palliative measures.

Previous literature has suggested that self-reported weakness and exhaustion could also be used in a frailty

determination[2] (along with physical measures), but this proved weak in the current study followed over a longer time. Another approach is to use deficit accumulation models, which do show increased adverse outcomes as the elderly acquire more problems, but are more difficult to record and quantify.

For now the most practical frailty assessment includes assessment of gait, physical activity, and weight loss—add them together with other deficits to evaluate those elderly most at risk for potentially modifiable adverse outcomes. This research gives us hope that our attempts to correct these issues may make a difference for our geriatric patients. ■

**References**


1. Abellan van Kan G, et al. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. *J Nutr Health Aging* 2008;12:29-37.
2. Fried LP, et al. Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56: M146-M156.


*Pharmacology Update*

# Fesoterodine Fumarate Extended Release Tablets (Toviaz™)


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

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*Drs. Chan and Elliott report no financial relationship to this field of study.*


THE FDA HAS APPROVED A NEW MUSCARINIC RECEPTOR antagonist for the treatment of overactive bladder. Fesoterodine is the prodrug of 5-hydroxymethyltolterodine. It is manufactured by Schwarz Pharma in Germany and distributed by Pfizer Labs as Toviaz™.

**Indication**

Fesoterodine is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

**Dosage**

The recommended initial dose is 4 mg once daily. The dose may be increased to 8 mg once daily depending on response and tolerability. The tablets should be swallowed whole and may be taken without regard to meals.[1] No dosage adjustment is recommended for patients with mild-to-moderate renal or hepatic insufficiency.[1]

**Potential Advantages**

Fesoterodine has low lipophilicity and therefore low CNS penetration. It also has low interpatient variability, which may result in more consistent and predictable clinical response.[2]

**Potential Disadvantages**

Similar to other drugs in the class, dry mouth is the most common adverse event. Other side effects include constipation, dry eyes, and difficulty urinating. Fesoterodine should not be used concomitantly with potent CYP3A4 inhibitors (e.g., clarithromycin, itraconazole).[1]

**■ COMMENTARY**

Fesoterodine is completely absorbed and is rapidly metabolized by nonspecific esterases to an active metabolite, 5-hydroxymethyltolterodine (5MHT). The active metabolite has high affinity for muscarinic receptors in the bladder compared to the salivary gland.[2] It also has lower lipophilicity compared to other available agents with the exception of trospium.[2] Its efficacy and safety were shown in two Phase III, randomized, double-blind, placebo-controlled, 12-week studies involving a total of 1903 subjects.[1,3,4] Subjects had symptoms of overactive bladder for 6 months or longer, at least 8 micturitions per day, at least 6 urinary urgency episodes, or 3 urge incontinences per 3-day diary period. The mean age of the subjects was 58 years and they were composed mainly of Caucasian (91%) women (79%). Subjects were randomized to fesoterodine 4 mg, 8 mg, or placebo. One study had an active control (tolterodine ER 4 mg).[4] The primary endpoints were the mean change in the number or urge urinary incontinence (UUI) episodes and the number of micturitions per 24 hours. Baseline UUIs were 3.7 for placebo, 3.8 and 3.9 for 4 mg, and 3.7 and 3.9 for 8 mg. Overall the mean reductions from baseline in the number of UUIs were 1.0 and 1.2, 1.77 and 2.06, and 2.27 and 2.42, respectively.[1] Baseline micturitions per 24 hours were 12.0 and 12.2 for placebo, 11.6 and 12.9 for 4 mg, and 11.9 and 12.0 for 8 mg. Mean reductions from baseline were 1.02, 1.74 and 1.86, and 1.94, respectively. Fesoterodine also improved health-related

quality of life.[5] The most common adverse event was mild-to-moderate dry mouth. The frequencies were 7% for placebo, 16% for 4 mg, and 34% and 36% for 8 mg. Fesoterodine 8 mg was more effective than tolterodine ER 4 mg daily in terms of UUIs per 24 hours but had a higher frequency of dry mouth (34% vs 17%).[4]

### Clinical Implications

Fesoterodine is the newest antimuscarinic agent approved for overactive bladder. It is not certain if this new agent offers any real clinical advantages over existing agents. In general, all these agents have shown moderate efficacy and improved health-related quality of life compared to placebo. However, relative efficacy among agents is not clear.[6] The adverse effects profile may differ, although the incidence of dry mouth appeared similar for extended release products. ■

### References


1. Toviaz Product Information. New York, NY: Pfizer Labs; April 2008.
2. Michel MC. Fesoterodine: A novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome. *Expert Opin Pharmacother* 2008;9:1787-1796.
3. Nitti VW, et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. *J Urol* 2007;178:2488-494.
4. Chapple CR, et al. Comparison of fesoterodine and tolterodine in patients with overactive bladder. *BJU Int* 2008;102:1128-1132.
5. Kelleher CJ, et al. Impact of fesoterodine on quality of life: Pooled data from two randomized trials. *BJU Int* 2008;102:56-61.
6. Chapple CR, et al. The effects of antimuscarinic treatments in overactive bladder: An update of a systematic review and meta-analysis. *Eur Urol* 2008;54:543-562.




## CME Questions

1. **Which of the following is *true* about accidental drug overdose in West Virginia?**
   a. Women were more likely to be victims of accidental overdose.
   b. Methadone was involved in more deaths than any other opioid.
   c. Alcohol was almost always involved.
   d. Doctor shopping was the primary means of obtaining the agent(s) involved.
2. **For a man older than age 65 diagnosed with low-grade prostate cancer, which of the following is most likely to cause death within 5 years?**
   a. Prostate cancer
   b. Motor vehicle accident
   c. Cardiovascular disease
   d. Cancer at another site
   e. Suicide
3. **Which of the following is *not* a useful criterion to establish frailty in the elderly, which is associated with potentially modifiable adverse outcomes?**
   a. Gait speed
   b. Physical activity
   c. Weight loss
   d. Exhaustion

**Answers:** 1. b, 2. c, 3. d.

## CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

# Clinical Briefs

*By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville*
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## Aspirin for all? Not so fast....

**Source:** Ogawa H, et al. Low dose aspirin for primary prevention of atherosclerotic events in patients with Type 2 diabetes. *JAMA* 2008;300:2134-2141.

THE SYLLOGISTIC PROCESS THAT LED us all to accept the utility of ASA in prevention of CVD in diabetics seemed innocent enough: a) ASA reduces CV events in persons with CVD, and b) diabetes is considered a CV risk equivalent; therefore, c) ASA must reduce CV events in persons with diabetes.

Things might not be as simple as they appear. First, despite the quite consistent advocacy for ASA to reduce CV events in persons without known CVD (i.e., primary prevention), such primary prevention has never been shown to reduce mortality. Second, although adult diabetics older than age 40 have similar or even greater risk of sustaining a myocardial infarction than a non-diabetic who has already had an MI, the mechanisms inducing MI might be different in diabetics than non-diabetics; we cannot assume that just because aspirin benefits one population, it will indeed benefit another population whose background risk factors differ (for instance, diabetics typically have smaller, more dense, more atherogenic LDL than non-diabetics).

Ogawa et al published a multicenter prospective randomized trial of ASA (81-100 mg/d) vs placebo in adult, Japanese Type 2 diabetics (n = 2539). None of the subjects had sustained a known CV event, and all were free of clinically manifest PAD at baseline. The primary endpoint of the trial was a composite of fatal and nonfatal CVD events, ACS, new angina, and TIA.

After a follow-up of 4.37 years (median), although there was a trend towards reduced atherosclerotic events in the ASA group, the results were not statistically significant. The conclusion of the authors: "….low-dose ASA as primary prevention did not reduce the risk of CV events." ■

## White coat hypertension: Not so innocent in Type 2 diabetes

**Source:** Kramer CK, et al. Impact of white coat hypertension on microvascular complications in Type 2 diabetes. *Diabetes Care* 2008;31:2233-2237.

THE PREPONDERANCE OF EVIDENCE about the impact of hypertension (HTN) on CV and renal (CV&R) endpoints is based upon measurement of BP in the office: so-called casual or office BP. For more than 3 decades, HTN specialists have recognized that office BP is only one way to view the burden of HTN. Indeed, either 24-hr ambulatory BP monitoring or even home BP self-monitoring correlates better with CV&R endpoints than office BP. One explanation for the inaccuracy of office BP is that some patients' BP rises when in the medical setting, yet remains essentially normal at other times. This phenomenon has been called white coat hypertension (WCH), and although some examiners have pointed out that WCH portends enhanced proclivity to develop frank hypertension, and ought to be considered of greater importance when target organ damage is present, others have opined that WCH exists, but if BP is otherwise normal, no intervention (save enhanced vigilance for the development of frank HTN) is necessary.

Kramer et al studied a population of Type 2 diabetics (DM2) comparing the prevalence of nephropathy and retinopathy in persons with WCH (n = 46) as compared to normotensives (n = 117).

DM2 subjects with WCH had a 2 times greater prevalence of nephropathy and 2.7 times greater prevalence of retinopathy (adjusted for confounders). Although the pathogenetic role played by WCH remains controversial, the associations discerned in this observational study merit concern. ■

## Relationship between vitamin K and insulin resistance

**Source:** Yoshida M, et al. Effect of vitamin K supplementation on insulin resistance in older men and women. *Diabetes Care* 2008;31:2092-2096.

CLINICIANS TRADITIONALLY ASSOCIATE vitamin K (VitK) with the coagulation system, especially as it relates to antithrombotic therapy with agents like coumadin. Although a biologically plausible mechanism remains to be identified, a recent observational study indicated a positive linear relationship between VitK and insulin sensitivity: Higher amounts of either dietary or supplemental VitK was associated with higher insulin sensitivity. Similarly, one small study indicated better glucose disposal (through better insulin sensitivity) after VitK supplementation in healthy men.

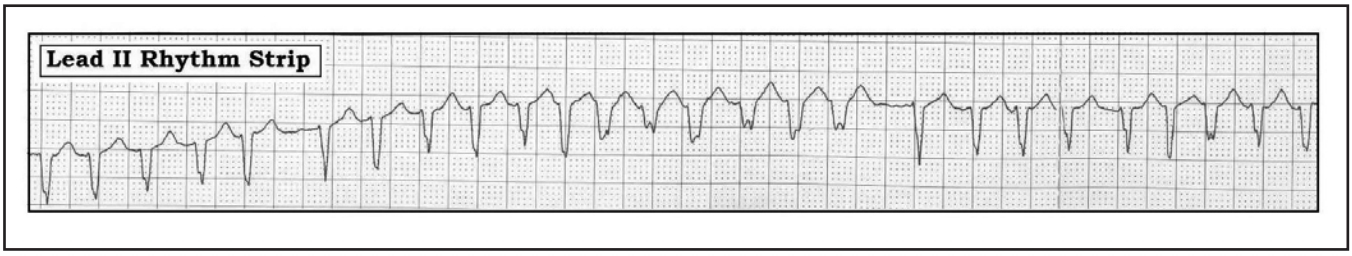
To investigate this phenomenon further, Yoshida et al studied healthy, non-diabetic adults (age 60-70; n = 355) by comparing levels of insulin resistance before and 36 months after VitK supplementation or placebo.

At the trial end, no changes were seen in levels of insulin resistance among female subjects. On the other hand, male subjects evidenced a statistically significant improvement in insulin resistance. Whether VitK supplementation might have a salutary effect in diabetics or others with overt insulin resistance syndromes (e.g., impaired glucose tolerance, obesity, polycystic ovary syndrome) remains to be clarified. ■

# How Wide Is the QRS?

***By Ken Grauer, MD,*** *Professor, Department of Community Health and Family Medicine, University of Florida*

*Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.*




**Scenario**

The lead II rhythm strip shown above was obtained from an elderly patient with shortness of breath. How wide is the QRS complex?

**Interpretation**

The answer as to how wide the QRS complex is in the above lead II rhythm strip is: "It depends." The underlying rhythm is rapid and irregularly irregular. No P waves are seen. Thus, the underlying rhythm is atrial fibrillation with a rapid ventricular response. Of interest is the constantly changing QRS duration and morphology throughout the rhythm strip. The QRS complex is at its most narrow immediately following the two relative pauses that occur in the rhythm strip. The first of these follows the fifth beat in the tracing. The second relative pause occurs a bit after the middle of the tracing. In both cases, QRS narrowing occurs after slight slowing of the rate.

This suggests that the tracing represents rapid atrial fibrillation with a rate-related bundle branch block conduction disturbance. The "width" of the QRS is dependent on the rate of the atrial fibrillation at the time in question. With rate-related conduction disturbances, bundle branch block tends to develop at a certain heart rate due to corresponding reduction in recovery time of the affected part of the conduction system. Interestingly, the rate of onset of the rate-related conduction disturbance often differs from the rate of offset. For example, QRS widening may develop at a heart rate of 120/min, but may not disappear until heart rate has dropped to a rate that is significantly below this (say to 100/min). Because the rate of onset and offset in any particular patient may vary, definitive diagnosis of the rhythm disturbance may at times be difficult.

In the above case, serial additional tracings on this patient confirmed that the underlying rhythm was truly atrial fibrillation, and that QRS widening was not reflective of ventricular ectopy, but rather of intermittent rate-related bundle branch block. Clues in support of this diagnosis are the irregular irregularity throughout the tracing with QRS narrowing immediately after the two relative pauses, and greatest QRS widening at times when the rate is at its most rapid. ■

## In Future Issues:

**Is Low-dose ASA of Value for Primary Prevention of Atherosclerotic Events in Type 2 Diabetes?**

**Predicting Incident Kidney Disease**

**Proton-pump Inhibitor Use and Risk of Community-acquired Pneumonia**

**Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-reactive Protein**