INTERNAL MEDICINE ALERT

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INSIDE

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Is Lower BP Always Really Better?

ABSTRACT & COMMENTARY

By Harold L. Karpman MD, FACC, FACP

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

Synopsis: *The risk of future cardiovascular events in patients with an acute coronary syndrome (ACS) was lowest when the BP was in the range of approximately 130-140 mmHg systolic and 80-90 mm Hg diastolic and became highest as the blood pressure became lower; in fact, a blood pressure less than 110/70 mm Hg may actually be dangerous.*

Source: Bangalore MD, et al. What is the optimal blood pressure in patients after acute coronary syndromes. *Circulation* 2010;122:2142-2151.

With respect to blood pressure (BP) readings in subjects without pre-existing cardiovascular disease, the concept that "lower is better" has become widely accepted by both physicians and patients because the data collected from observational studies involving more than 1 million individuals has suggested that the rate of occurrence of both ischemic heart disease and stroke increase progressively and linearly with increasing blood pressure.[1] In fact, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure very clearly stated that "the relationship between BP and risk of cardiovascular events is continuous, consistent, and independent of other risk factors" and concluded that a BP less than 120/80 mmHg should be considered "optimal" or "normal."[2,3]

This linear theory, which might hold true for the general population, has been challenged for many years, especially for diastolic blood pressure, in patients with stable coronary artery disease because the relationship between BP and cardiovascular outcomes has been demonstrated in some studies to follow J- or U-shaped curves with higher event rates at both very low and very high BP determinations.[4-6] The

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results of these studies have been quite controversial and, in fact, the Seventh Report of the Joint National Committee indicated that "there is no definitive evidence of an increase in risk of aggressive treatment unless the diastolic BP is lowered to less than 50 or 60 mmHg by treatment."[2] Finally, the American Heart Association scientific statement, Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease, recommended a target BP less than 130/80 mmHg for patients at high risk of coronary artery disease and acute coronary syndromes, but it was acknowledged that there were limited data to support this recommendation.[7]

Because of all the confusion and limited data on what the most desirable blood pressure should be in patients suffering from ACS, Bangalore and his colleagues (including the PROVE-IT TIMI 22 Trial Investigators) analyzed what data exist regarding the best target range of BP in patients who have experienced an ACS. They analyzed the 4162 patients enrolled in the Pravastatin or Atorvastatin Evaluation and Infection Therapy — Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 Trial.[8,9] They concluded that, after an acute coronary syndrome, a J- or U-curve association existed between the BP reading and the risk of future cardiovascular events, with the lowest event rates occurring in the BP range of approximately 130-140 mmHg systolic and 80-90 mmHg diastolic, and that a relatively flat curve was present for systolic pressures of 110-130 mmHg and diastolic pressures of 70-90 mmHg. They further suggested that too low a BP (especially less than 110/70 mmHg) may actually be dangerous.

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Questions & Comments
Please call **Paula Cousins**, Senior Managing Editor, at (404) 262-5488.

■ COMMENTARY

The results of the analysis conducted by Bangalore and his colleagues are really quite interesting. They demonstrated that in the high-risk, post-ACS population of the PROVE-IT-TIMI 22 trial, a J- or U-shaped relationship existed between BP and the risk of poor cardiovascular outcomes and an exponential increase in the event rates occurred at both the high and the low BP values. Their analysis revealed that the event rate was the lowest when the BP was in the range of 136/85 mmHg and that unimpressive or flat event rates occurred in patients with systolic pressures of 110-130 mmHg and diastolic pressures of 70-90 mm Hg. Finally, they pointed out that a BP less than 110/70 mm Hg was associated with an increased risk of cardiovascular events, suggesting that a very low BP identifies the subset of patients with a poor prognosis. Therefore, it is important to point out that the evidence supporting lower BP targets is lacking,[10,11] suggesting that the frequently quoted paradigm of "lower is better" in BP control is not applicable to ACS patients beyond a certain BP target level. The Bangalore results are consistent with other trials, which have demonstrated no benefit of more intensive BP management beyond standard lowering of BP to less than 140/90 mmHg; the study results clearly extend this observation to the high-risk group of post-ACS patients.

In summary, lowering the systolic BP to less than 140/90 mmHg is obviously important in all patients, but especially in those patients with an ACS. However, lowering the BP to 110/70 mmHg or lower may not be helpful, and may, in fact, be harmful. The bottom line is that BP that is too low is not better in ACS patients. ■

References

1. Lewington S, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-1913.
2. Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; the JNC 7 report. *JAMA* 2003;289:2560-2572.
3. The sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413-2446.
4. Cruickshank JM, et al. The benefits and potential harm of lowering high blood pressure. *Lancet* 1987;1:581-584.
5. Messerli FH, et al. Dogma disputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144:884-893.
6. Protogerou AD, et al. Diastolic blood pressure and mortality in the elderly with cardiovascular disease.

Hypertension 2007;50:172-180.
7. Rosendorff C, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: A scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007;115:2761-2788.
8. Cannon CP, et al. Design of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)-TIMI 22 trial. *Am J Cardiol* 2002;89:860-861.
9. Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-1504.
10. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-1585.
11. Arguedas JA, et al. Treatment blood pressure targets for hypertension. *Cochrane Database Syst Rev* 2009;(3):CD004349.

Early to Bed? Maybe Not Such a Good Idea

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a consultant for Cephalon, and serves on the speakers bureaus for Resmed and Respironics.

Synopsis: *Brief behavioral intervention significantly relieved insomnia in a group of older adults.*

Source: Buysse DJ, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med* 2002 Jan 24; Epub ahead of print.

This report is the result of a randomized trial of 79 adults, mostly women, whose mean age was about 72 years. Subjects were recruited from newspaper ads and clinics, and were self-identified with insomnia. To be included in the study, participants had to have a sleep complaint lasting for at least a month, adequate opportunity and circumstances for sleep, and significant distress or daytime impairment. Consistent with most clinical definitions of insomnia, there were no requirements for objective documentation of sleep latency, duration, or disturbance for inclusion in the study (though these things were measured and used as outcome measures). Insomnia was (as it usually is) defined simply on the basis of the patients' dissatisfaction with their sleep.[1,2] Potential participants were excluded if they had dementia, untreated psychiatric, substance use, or other sleep disorders, recent hospitalization, ongoing cancer treatment, or life expectancy less than 6 months. These investigators did not exclude those with treated depressive or anxiety disorders (the two conditions most commonly associated with chronic insomnia[2,3]).

After screening, participants were randomized to either an Information Control (IC) or a Brief Behavioral Therapeutic Intervention (BBTI). This Behavioral Intervention included a 45- to 60-minute individual session followed by a 30-minute follow-up session 2 weeks later and 20-minute telephone calls after weeks 1 and 3. The Behavioral Intervention (which was called BBTI by the authors of this paper) included sleep education and four main recommendations: 1) reduce time in bed; 2) get up at the same time every day, regardless of sleep duration; 3) do not go to bed unless sleepy; and 4) do not stay in bed unless asleep. Napping was discouraged. Total time in bed was limited to average self-reported sleep time + 30 minutes, with a minimum of 6 hours. The Information Control group got three fairly standard pamphlets (with content that overlapped that received by the BBTI group) and a brief follow-up phone call. All the interventions were delivered by a single master's level mental health nurse practitioner. Participants completed a variety of questionnaires and diaries, and underwent polysomnography (sleep study) and actigraphy (indirect measure of sleep) at the beginning and 6 months after the intervention.

There were several possible criteria for improvement: 1) response (change in the Pittsburgh Sleep Quality Index score of ≥ 3 points or increase in sleep diary sleep efficiency of ≥ 10%); 2) remission (response criterion plus final Pittsburgh Sleep Quality Index score of < 5 and sleep diary sleep efficiency of > 85%, corresponding to "good sleep" values; 3) partial response (improvement in Pittsburgh Sleep Quality Index or sleep efficiency but worsening in the other measures); and 4) nonresponse (change in Pittsburgh Sleep Quality Index of < 3 points and increase in sleep diary sleep efficiency of < 10%). These are reasonable criteria, given the subjective, self-reported nature of insomnia itself.

The BBTI produced significantly better outcomes in self-reported sleep and health, sleep diary, and actigraphy (all $P < 0.001$), but not polysomnography. Improvements were maintained at 6 months.

Categorically defined response improvement and the proportion of participants without insomnia (55% vs 13%) were significantly higher for BBTI than for IC. The number needed to treat was 2.4 for each outcome. No differences were found according to hypnotic or antidepressant use, sleep apnea, or recruitment source.

■ **COMMENTARY**

This was a real world study! Older women with self-reported sleep complaints and likely underlying mood disturbance make up the largest group of insomniacs in practice,[2,4] as they did in this study. The authors measured sleep objectively, but defined insomnia response based on self-report, as typically happens in clinical practice. And the time investment by clinicians (about 2 hours) was not extreme. Furthermore, the actual intervention was performed by a nurse practitioner. This is doable! The behavioral interventions used by the investigators are based on established principles of sleep restriction and stimulus control techniques, the efficacy of which has been well documented.[5,6] Notably, a key component of the behavioral intervention was to get participants to spend less time in bed, which should increase sleep homeostatic pressure and reduce the conditioned anxiety associated with being in bed not sleeping. Older adults tend to fall asleep earlier, which may lead to middle of the night wakefulness. Indeed, middle of the night wakefulness (biphasic sleep) may have been common in our ancestors and may be a normal response to long winter nights.[7,8] However, our current culture views this with alarm. Reassurance and a later bedtime are probably as effective and certainly safer than chronic use of sleeping pills in the older population.[9] ■

References

1. American Academy of Sleep Medicine. *The International Classification of Sleep Disorders: Diagnostic and Coding Manual.* 2nd ed. Darien, IL: American Academy of Sleep Medicine; 2005.
2. Ohayon MM. Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Med Rev* 2002;6:97-111.
3. Simon GE, VonKorff M. Prevalence, burden, and treatment of insomnia in primary care. *Am J Psychiatry* 1997;154:1417-1423.
4. Taylor DJ, et al. Comorbidity of chronic insomnia with medical problems. *Sleep* 2007;30:213-218.
5. Smith MT, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry* 2002;159:5-11.
6. Morin CM, et al. Nonpharmacological interventions for insomnia: A meta-analysis of treatment efficacy. *Am J Psychiatry* 1994;151:1172-1180.
7. Ekirch AR. Sleep we have lost: Pre-industrial slumber in the British Isles. *Am Hist Rev* 2001;106:343-386.
8. Wehr TA. In short photoperiods, human sleep is biphasic. *J Sleep Res* 1992;1:103-107; doi:10.1111/j.1365-2869.1992.tb00019.x.
9. Glass J, et al. Sedative hypnotics in older people with insomnia: Meta-analysis of risks and benefits. *BMJ* 2005;331:1169-1174.

Brief Reports

A Review of Current Clinical Stroke Literature

By Matthew E. Fink, MD

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

These reports originally appeared in the February issue of Neurology Alert. *At that time it was peer reviewed by M. Flint Beal, MD, Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center, New York, NY. Dr. Beal reports no financial relationship to this field of study.*

Risk of Stroke and CV Death from NSAIDs

Source: Trelle S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta-analysis. *BMJ* 2011;342:c7086; doi:10.1136/bmj.c7086.

The authors reviewed all large-scale randomized controlled clinical trials comparing any NSAIDs or placebo, and performed a meta-analysis looking at the rates of myocardial infarction, stroke, death from cardiovascular cause, and death from any cause. They reviewed 31 trials in 116,429 patients with more than 115,000 patient years of follow-up. Patients were allocated to naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib, or placebo.

Compared with placebo, rofecoxib was associated with the highest risk of myocardial infarction (rate ratio [RR], 2.12; 95% confidence interval [CI], 1.26-3.56). Ibuprofen was associated with the highest risk of stroke (RR, 3.36; 95% CI, 1.00-11.6), followed by diclofenac. Naproxen was associated with the lowest risk of stroke (RR, 1.76; 95% CI, 0.91-3.33) and its use was not associated with an increased risk of cardiovascular death. It appears that the entire class of NSAIDs is associated with an increased risk of cardiovascular events, and alternatives should be considered in the management of pain.

Do Patients with Isolated Vertigo Have a Higher Risk for Stroke?

Source: Lee CC, et al. Risk of stroke in patients hospitalized for isolated vertigo. *Stroke* 2011;42:48-52.

In a study from Taiwan, all patients hospitalized with a principal diagnosis of vertigo (n = 3021) were compared to an age- and sex-matched control group of patients hospitalized for appendectomy, and the two cohorts were followed for 4 years to ascertain cardiovascular risk factors and subsequent stroke.

During the 4-year follow-up period, 185 (6.1%) patients from the study group were admitted with stroke, and 58 (1.9%) from the control group had a stroke. The vertigo group had statistically significantly higher rates of hypertension, diabetes, coronary disease, and hyperlipidemia, and the risk of stroke was determined by the presence of these risk factors, plus age > 55 years and male sex. The patients were divided into three groups, based on risk factors, and the 4-year cumulative risks for stroke were 1.9 (no risk factors), 7.7 (1-2 risk factors), and 14 (3 or more risk factors). Vertigo may be a clinical symptom of vertebrobasilar disease and cardiovascular risk factors should be identified and treated to prevent future stroke. Isolated vertigo, without these risk factors, is rarely associated with any type of stroke.

Stroke Type May Determine Outcome after Treatment with Thrombolysis

Source: Mustanoja S, et al. Outcome by stroke etiology in patients receiving thrombolytic treatment. descriptive subtype analysis. *Stroke* 2011;42:102-106.

In a population-based study from Helsinki, Finland, investigators looked at outcomes after intravenous thrombolysis from a single hospital from 1995 to 2008, and analyzed outcomes based on stroke type, using a multivariate logistic regression. Good outcome was defined as modified Rankin Scale ≤ 2. Stroke classification was based on the TOAST trial.

Of 957 ischemic stroke patients treated with intravenous thrombolysis, 41% (389) had cardioembolism, 23% (217) had large-artery atherosclerosis, and 11% (101) had small vessel disease (SVD). A good outcome was more common with SVD than with any other subtype. Patients with SVD were more often male, had a lower baseline NIH Stroke Scale (NIHSS) score, lower mortality, and no episodes of intracranial hemorrhage. Common vascular risk factors — hypertension, diabetes, hypercholesterolemia, and transient ischemic attacks — were equally distributed across all stroke subtypes. After adjustment for baseline NIHSS, glucose level, and hyperdense artery sign, patients with SVD still had better outcomes. ■

Pharmacology Update

Fentanyl Sublingual Tablets (Abstral®) CII

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

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

The FDA has approved a new formulation of fentanyl for the management of breakthrough pain in cancer patients. The fasting-acting, rapidly disintegrating, sublingual tablet is marketed by ProStrakan Inc. as Abstral®. It currently is approved in Sweden, the United Kingdom, France, and Germany.

Indications

Fentanyl sublingual tablets are indicated only for the management of adult cancer patients with breakthrough pain who are currently receiving opioid therapy for their underlying persistent cancer pain.[1] Use is for opioid-tolerant patients, meaning that they are taking at least 60 mg/day of oral morphine, 25 mcg/hour of transdermal fentanyl, 30 mg/day of oxycodone, 8 mg of hydromorphone, and 25 mg of oxymorphone, or other equivalent opioid for a week or longer.[1]

Dosage

The initial dose is 100 mcg (placed under the tongue on the floor of the mouth) and should be titrated to a tolerable effective dose. No more than two doses can be taken for each breakthrough pain episode.[1] There should be at least a 2-hour period between treatment episodes and no more than 4 episodes per day once a successful dose is identified. All patients should be started at 100 mcg. Sublingual fentanyl should not be converted from other formulations of fentanyl on a mcg-per-mcg basis.

Fentanyl sublingual tablets are available as 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg strengths.

Potential Advantages

Sublingual fentanyl is a potent analgesic with a rapid onset and short duration of action.

Potential Disadvantages

Sublingual fentanyl is contraindicated in opioid non-tolerant patients. Life-threatening respiratory depressant can occur at any fentanyl dose in these patients.[1] In the clinical trial, approximately 40% withdrew during the titration phase either due to intolerance or inability to achieved an effective dose; only 60% of patients were able to successfully reach a stable and effective dose.[2]

Comments

Fentanyl is formulated as a rapid-onset sublingual tablet for the treatment of breakthrough cancer pain. Fentanyl is well absorbed from the oral mucosa. The efficacy was shown in a randomized, placebo-controlled, phase III study in adult patients with breakthrough cancer pain. This type of pain is characterized by rapid onset, short duration, and severe intensity. Study participants (n = 131) initially entered a 2-week titration phase to identify an effective dose (100-800 mcg). An effective dose was defined as pain relief for all episodes over 2 consecutive days. They then entered a 2-week, double-blind phase during which patients received 10 doses (seven doses of the identified effective dose and three matching placebo) taken in random order with placebo doses separated by at least one active dose. The primary endpoint was mean sum of pain intensity from baseline (SPID) over 30 minutes. Secondary endpoints include SPID over 60 minutes, pain intensity difference, percent responders (≥ 30% reduction in pain intensity in at least one episode), overall satisfaction, and use of rescue medication. The median dose was 600 mcg with a median of three doses per day. Sublingual fentanyl showed significant improvement in SPID at 30 minutes. This was evident within 10 minutes and was maintained over the 60-minute assessment period. Approximately 47% of patients were satisfied or very satisfied with the formulation and 11% required rescue medication while on active drug compared to 27% on placebo. The percent responders were 87% vs 65%. The most frequently reported adverse effects were nausea (12%), vomiting (5.3%), and somnolence (4%). Patients have been treated for up to 12 months.[3]

Clinical Implications

Sublingual fentanyl offers a rapid onset and potent analgesic for breakthrough cancer pain. Enrollment in a Risk Evaluation and Mitigation Strategy program is required for any pharmacy, distributor, or health-care professional involved in the distribution or use of Abstral. ■

References

1. Abstral Prescribing Information. Bedminster, NJ: ProStrakan Inc.; January 2011.
2. Rauck RL, et al. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. *Curr Med Res Opin* 2009;25:2877-2885.
3. Nalamachu S, et al. Long-term safety and tolerability of sublingual fentanyl. American Academy of Pain Medicine 25th Annual Meeting; Honolulu, HI; Jan. 28-31, 2009.

CME Questions

8. **After an acute coronary syndrome, the risk of future cardiovascular events:**
   a. bears no relationship to the measured BP.
   b. was lowest when the BP was in the range of approximately 130-140 mm Hg systolic and 80-90 mm Hg diastolic.
   c. was highest when the systolic BP was in the range of 110-130 mm Hg.
   d. was lowest when the BP was less than 110/70 mm Hg.

9. **Effective behavioral intervention for insomnia:**
   a. must be delivered by an MD or PhD.
   b. should be coupled with an FDA-approved hypnotic.
   c. includes reducing time in bed.
   d. is not feasible in older adults.

Answers: 8. b, 9. c.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
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Rifaximin for IBS without constipation

Source: Pimentel M, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011;364:22-32.

It has been recognized for more than a decade that most patients with IBS have abnormal lactulose hydrogen breath test results, consistent with small bowel bacterial overgrowth. Neomycin treatment, which can re-establish bowel flora, has shown modest efficacy in IBS, but is limited by tolerability issues. Other systemic antibiotics have not provided consistent symptomatic improvement in IBS. A previous pilot trial of rifaximin found that 10 days of treatment provided symptomatic improvement as measured 10 weeks later.

The TARGET trials are two identical double-blind, placebo-controlled trials of subjects with IBS without constipation. Patients were randomly assigned to rifaximin 550 TID or placebo for 2 weeks. Symptoms were monitored for up to 10 weeks. The primary outcome was the proportion of individuals reporting adequate relief of global IBS symptoms. The main secondary outcome was relief of bloating. Additional outcomes included abdominal pain and stool consistency.

Rifaximin provided a statistically significant improvement in global symptoms, bloating, abdominal pain, and stool consistency. Consonant with a very favorable tolerability profile seen in prior clinical trials, the safety profile of rifaximin was similar to placebo in this report. It is anticipated that systemic effects of rifaximin will be rare, since only a miniscule proportion of administered drug enters the systemic circulation.

Short-term treatment with rifaximin can provide statistically significant improvements for patients with IBS without constipation. ■

Pre-exposure HIV prophylaxis for men who have sex with men

Source: Grant RM, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;363:2587-2599.

Men who have sex with men (MSM) are a high-risk group for acquisition of HIV, but other than safe sex practices, there has been little encouraging information about chemoprophylaxis. Certainly clinicians have some degree of confidence in the efficacy of post-exposure HIV prophylaxis post-needle stick in the health care setting, but the only population in which pre-exposure prophylaxis has been studied utilized tenofovir vaginal gel in women in Africa, reporting a 39% reduction in HIV infection.

HIV-seronegative men (or transgender women) who have sex with men (n = 2499) were randomized to a combination antiretroviral treatment (emtricitabine and tenofovir) or placebo once daily. They were followed for up to 2.8 years (median 1.2 years).

During follow-up, all subjects were seen every 4 weeks, during which they were counseled on safe sex practices, sexually transmitted diseases (STDs), and STD risk reduction.

At the conclusion of the trial, 36 of 1224 pre-exposure prophylaxis patients sero-converted vs 64 of 1217 placebo subjects (a 44% reduction in HIV incidence). Tolerability of the active antiviral treatment was excellent. The risk reduction demonstrated in this trial seems all the more remarkable because the reduction in unsafe sex practices attributed to the repetitive sexual health education and counseling during the trial would tend to minimize benefits of the medication. ■

Gait speed and survival in older adults

Source: Studenski S, et al. Gait speed and survival in older adults. *JAMA* 2011;305:50-58.

The frailty of senior citizens is often portrayed on-stage by slow, stiff gait. This representation may be much more than theatre. Indeed, according to this pooled analysis of a very large data set (34,485 community-dwelling senior citizens), gait speed is linearly associated with mortality among persons age 65 years and older.

Gait speed in the studies was calculated by timing the study subjects while they walked distances varying from 2.4 to 6 meters by simply dividing the distance covered by elapsed time, recorded as meters/second. After obtaining baseline gait speed, study subjects were followed for 6-21 years.

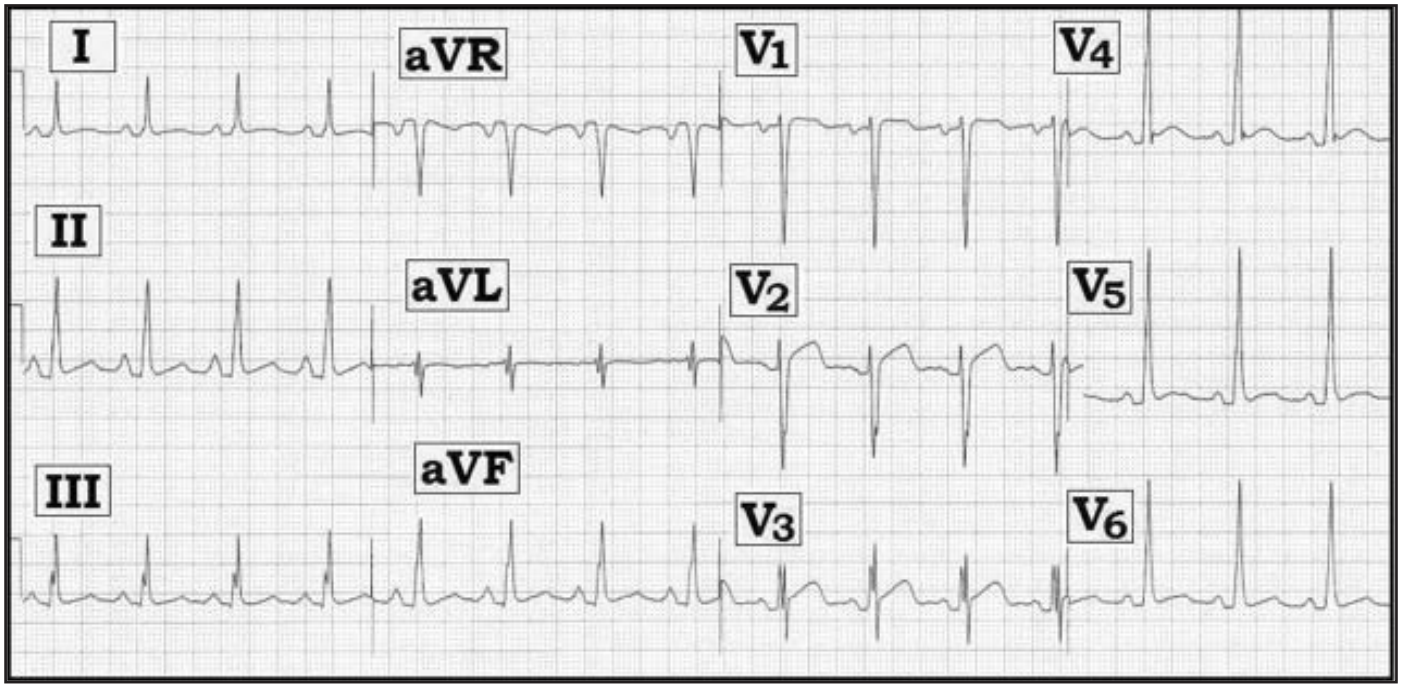
For each 0.1 meter/second increase in baseline gait speed, there was a 12% higher rate of survival. This was independent of gender, BMI, smoking, blood pressure, or self-reported health.

Should clinicians wish to consider using gait speed as a health predictor, the method is simple: The patient is asked to walk over a predetermined distance with the instructions "Walk at your usual pace, as if you were walking down the street." No particular encouragement or stimulus to promote intensification of effort is necessary. ■

History Is Everything

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: Interpret the ECG above, obtained from a patient presenting to the Emergency Department. Is there any cause for concern?

Interpretation: The ECG shows sinus rhythm at 85/minute. The PR interval is normal. The QRS duration is upper normal (half a large box, but not more) and the QT interval is upper normal (about half the R-R interval, with a QTc ≈ 0.44 second). The axis is normal (+70°). There is right atrial abnormality (tall, peaked P wave in lead II ≥ 2.5 mm); possible left atrial abnormality (minimally deep negative component to the P in lead V_1); and left ventricular hypertrophy (S in $V_{1,2}$ + R in $V_{5,6}$ ≥ 35 mm). Regarding Q-R-S-T changes, there is at most a tiny q in lead III, and transition is normal (between V_2 to V_4). The most remarkable finding on this tracing are the ST segments, which manifest at least 2 mm of J point elevation with straight (if not coved) takeoff in leads V_2,V_3. There is slight elevation with J point notching in lead V_4. Missing from this presentation is the history and mention of prior tracings for comparison. At the very least we suspect multichamber enlargement and a probable cardiomyopathy. If the patient had new-onset chest pain, acute coronary syndrome with ST elevation would have to be ruled out. If ECG findings were chronic, ST-T changes from medication effect, early repolarization, cardiomyopathy, or some combination of these would have to be considered. History is everything in the interpretation of this tracing. ■

In Future Issues:

Effect and Safety of Intensive LDL Lowering

Long-term Safety of Statin Treatment in Patients with Abnormal Liver Tests

Association of Plasma β-Amyloid and Cognitive Decline