AHC Media

Internal Medicine

Vol. 37, Issue 17, September 15, 2015
AHCMedia.com

Evidence-based summaries of the latest research in internal medicine [ALERT]

ABSTRACT & COMMENTARY

Spice is Nice

By Joseph E. Scherger, MD, MPH

Vice President, Primary Care, Eisenhower Medical Center; Clinical Professor, Keck School of Medicine, University of Southern California

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

SYNOPSIS: The habitual consumption of spicy foods is associated with reduced mortality independent of other risk factors for death.

SOURCE: Lv J, et al. Consumption of spicy foods and total and cause specific mortality: Population-based cohort study. *BMJ* 2015;351:h3942.

A group of Chinese investigators conducted a prospective cohort study between 2004 and 2008 and followed 512,891 adults aged 30-79 years to until the end of 2013. Participants completed a questionnaire and were divided into four groups based on their reported intake of spices: never, 1-2 days/week, 3-5 days/week, and 6-7 days/week. The spices identified were fresh chili pepper, dried chili pepper, chili sauce, chili oil, and other spices. Ten survey sites were resurveyed in 2008 to confirm the continued intake of spices. Other risk factors for death, such as socioeconomic status, lifestyle behaviors, nutritional intake, presence of chronic conditions, body mass index, fasting blood glucose, and blood pressure, also were measured.

Local health insurance databases were used to determine death and its causes. Seven categories of death were used: cancer, ischemic heart disease, cerebrovascular disease, diabetes mellitus, respiratory disease, infections, and other causes.

The results show that participants who ate spicy foods 6 or 7 days a week showed a 14% relative risk reduction in total mortality compared with those who ate spicy foods less than once a week. Any regular consumption of spices reduced mortality. The reduction was seen in deaths from cancer, ischemic heart disease, and respiratory

Financial Disclosure: *Internal Medicine Alert*'s editor Stephen Brunton, MD, is a retained consultant for Abbott, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, Sanofi, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Contributing editor Louis Kuritzky is a retained consultant for AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chelsea, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and associate managing editor Jonathan Springston report no financial relationships relevant to this field of study.

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Internal Medicine Alert,
ISSN 0195-315X, is published monthly by
AHC Media, LLC
One Atlanta Plaza,
950 East Paces Ferry Road NE, Suite 2850
Atlanta, GA 30326.
AHCMedia.com

GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Internal Medicine Alert*, P.O. Box 550669, Atlanta, GA 30355.

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disease. No associations were significant in the other causes of death. Men and women showed a similar risk reduction.

■ COMMENTARY

Spices have a long history in the culinary world, and the spice trade is part of the history of civilization. There is a worldwide trend of increased use of spices as flavorings in foods.[1,2] In China, chili pepper is among the most popular spicy foods consumed.

Beneficial effects of spices have been studied, and their bioactive ingredients, such as capsaicin, have been shown to reduce cancer.[2-4] Red pepper has been found to decrease appetite and reduce the rate of overweight and obesity.[5] Spices exhibit antibacterial activity and have an impact on gut microbiota in a way that may reduce the risk of diabetes, cardiovascular disease, liver cirrhosis, and cancer.[6-8]

This study reinforces the emerging science that suggests our nutrition should focus on the wisdom of the ages more than on recent processed foods. Spices have a place among the healthy ingredients of a cuisine. Like with coffee and tea, it is nice when culinary pleasure combines with better health. ■

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ABSTRACT & COMMENTARY

Are Premature Ventricular Contractions Dangerous?

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: In a population-based sample, a higher frequency of premature ventricular contractions was associated with a decrease in left ventricular ejection fraction, an increase in incident congestive heart failure, and an increase in mortality.

SOURCE: Dukes JW, et al. Ventricular ectopy as a predictor of heart failure and death. *J Amer Coll Card* 2015;66:101-109.

The effect of premature ventricular contraction (PVC) frequency on left ventricular systolic function, incident congestive heart failure (CHF), and/or mortality in the general population remains unknown. Because of individual variations in the frequency of PVCs during a 24-hour period, Holter monitoring for at least 24 hours is essential to accurately assess the frequency of daily PVCs and to attempt to determine which periodic events may contribute to the true PVC burden.[1,2] Dukes et al[3] used a 24-hour Holter monitor to ascertain PVC frequency in an attempt to determine if PVC frequency was a predictor of a decrease in the left ventricular ejection fraction (LVEF), incident CHF, and/or

death in a population-based cohort study.

Dukes et al studied 1139 Cardiovascular Health Study participants who were randomly assigned to 24-hour ambulatory electrocardiography monitoring and who had a normal LVEF and no history of CHF. PVC frequency was quantified using Holter studies, and LVEF was measured from an echocardiogram recorded at baseline and on echocardiograms obtained 5 years later in participants who were followed for incident CHF and/or death. Participants who were in the upper quartile vs the lower quartile of PVC frequency had a multivariable-adjusted three-fold greater odds of a 5-year decrease in LVEF, a 48% increased risk of developing incident CHF, and a 31% increased risk of death during a median follow-up of > 13 years. The specificity for the 15-year risk of CHF exceeded 90% when PVCs comprised at least 0.7% of the total number of heartbeats. The positive predictive value for the 15-year risk of incident CHF was > 50% when the percentage of PVCs was between 1.24% and 3.55% of all cardiac beats.

■ COMMENTARY

The results of the Dukes study are very important in that they demonstrate that a higher frequency of PVCs is associated with a significant decrease in LVEF, an increase in incident CHF, and an increase in mortality, which is at least partly explained by the increased frequency of CHF. These findings are quite important because CHF currently affects more than 5 million Americans and its prevalence is expected to increase by 25% within the next 15 years.[4] Equally important, up to 50% of CHF cases have no known etiology.[5] Some known risk factors for CHF, such as advanced age, are not treatable; however, other risk factors, such as hypertension, obesity, and some effects of progressive coronary artery disease, are treatable. The results of the Dukes study suggest that PVCs may be an important cause of an occult or "idiopathic" cardiomyopathy, which may lead to CHF and an increased incidence of cardiovascular death; however, one cannot exclude the possibility that the presence of PVCs may be a marker of an abnormality in people who have occult cardiomyopathy of any etiology. The mechanism by which frequent PVCs lead to systolic dysfunction remains unknown; however, the available evidence favors adverse ventricular remodeling that occurs due to repeated dysynchrony.[10,11] Furthermore, recent studies have demonstrated that systolic dysfunction in patients with CHF may improve and be resolved after successful ablation of high-burden PVCs.[6-9] At this time, recognizing that there is a high prevalence of PVCs in the general population, there is no scientific proof that suppressing the high prevalence of PVCs will reduce the incidence of CHF and improve longevity. Certainly, this is the question that should be answered by setting up a properly structured, carefully controlled study to determine if the suppression of the high incidence of PVCs in the general population will reduce the incidence of CHF and/or cardiovascular death in the general population.

For the time being, clinicians should be aware of the results of the Dukes study and decide whether to consider treating excessive numbers of PVCs, which they have determined to be present in individual patients, with medical or ablation therapy, although the research results that would mandate such therapy are not available as yet and future research is required before entertaining this treatment approach in clinical practice. ■

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ABSTRACT & COMMENTARY

Antibiotics for Acute Appendicitis

By Richard R. Watkins, MD, MS, FACP

Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH

Dr. Watkins has received research support from Forest Pharmaceuticals.

SYNOPSIS: A randomized, multicenter clinical trial compared antibiotic therapy to surgery for uncomplicated acute appendicitis and found most patients who received antibiotics did not require appendectomy during the 1-year follow-up period. Of those who needed surgery after treatment with antibiotics, the risk for complications was low.

SOURCE: Salminen P, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis. *JAMA* 2015;313:2340-2348.

Appendectomy has been the treatment for acute appendicitis since the late 19th century. During the past decade, the notion of treating acute appendicitis with antibiotics alone has been proposed and evaluated in several clinical trials. However, these trials have been criticized because of methodological limitations. Therefore, Salminen et al aimed to test the hypothesis that acute appendicitis could be successfully treated with antibiotics and surgery avoided using a more robust study design that would overcome the limitations of previous trials.

The study was a randomized, open-label, noninferiority clinical trial conducted at six Finnish hospitals between 2009 and 2012. Inclusion criteria were patients between 18 and 60 years of age who presented to the emergency department (ED) with clinical symptoms of acute appendicitis confirmed by CT scan. Those with complicated appendicitis, including perforation, presence of an appendicolith, abscess, or tumor, were excluded. Randomization was performed with a 1:1 allocation ratio for either open appendectomy or antibiotic therapy. Ertapenem was given to those patients in the antibiotic treatment group for 3 days, with the first dose given in the ED. Following intravenous therapy, oral levofloxacin and metronidazole were prescribed for 7 days. The primary endpoint in the antibiotic group was resolution of appendicitis without surgery and no recurrent appendicitis over the next 1 year. The secondary endpoints were overall post-intervention complications, late recurrence (more than 1 year) of acute appendicitis after antibiotic therapy, length of hospital stay, length of sick leave used by the patient, and post-intervention pain issues.

Of the 530 patients randomized, 273 underwent appendectomy and 257 were assigned to antibiotic therapy. After one year, 186 patients in the antibiotic group did not require appendectomy (72.7%), while 70 patients did (27.3%). Moreover, despite having recurrent appendicitis and delayed operation, the surgical complication rate for the patients in the antibiotic group who eventually needed an appendectomy was 7% compared to 20.5% in the surgical group ($P = 0.02$). The overall complication rate was also significantly lower in the antibiotic group (2.8% vs 20.5%, $P < 0.001$). Length of hospitalization was similar between the groups (median, 3 days), while pain scores and length of sick leave (median 19 days vs 7 days) favored the antibiotic group. At the beginning of the study, the investigators established 24% as the minimum clinically important difference between the treatment groups. The intention-to-treat analysis revealed a difference of -27%, meaning the results did not demonstrate noninferiority of antibiotic therapy relative to surgical therapy ($P = 0.89$).

■ COMMENTARY

The findings of Salminen et al support the hypothesis that many patients with acute appendicitis can be treated with antibiotics alone, and even the ones who fail antibiotic therapy and eventually undergo appendectomy will likely have an uncomplicated course. A particular strength of the study was the reliance on CT scans to diagnose acute appendicitis. This has proven to be a more accurate method to diagnose appendicitis than older ones, i.e., history and physical examination. The use of CT scans minimized diagnostic uncertainty in the trial and allowed for exclusion of intraluminal appendicoliths, which can lead to complicated acute appendicitis. A potential use of these data could be to serve as the basis of a scoring system that would help clinicians determine which patients should undergo appendectomy and which should be treated with antibiotics alone.

Although this was a seminal study, one limitation

was that antibiotic therapy did not prove to be noninferior to surgical intervention, which is currently the standard of care. My suspicion is that this was due methodological reasons and not from a true weakness of antibiotics per se. For example, the investigators had difficulty enrolling patients in the trial, necessitating a re-evaluation of the sample size that may have led to underpowering and indeterminate results. Further studies are needed to conclusively validate the findings of Salminen et al. How will this study impact clinical practice? There is now good evidence that select patients with acute uncomplicated appendicitis (i.e., not pregnant, older than 18 years, not systemically ill) diagnosed by CT scan can be successfully treated with antibiotics (intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and metronidazole) with close follow up. While we wait on additional studies, antibiotic therapy instead of immediate appendectomy seems to be a reasonable option that can be discussed with some patients who present to the ED with acute appendicitis. ■

PHARMACOLOGY UPDATE

Sacubitril and Valsartan Tablets (Entresto)

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 relationships relevant to this field of study.

The combination of the sacubitril and valsartan has been approved by the FDA for the treatment of heart failure. Sacubitril is a prodrug for the neprilysin inhibitor, LBQ657. Neprilysin is an enzyme that metabolizes natriuretic peptides (NP). Valsartan, an angiotensin II receptor type 1 antagonist (ARB), has been available since 2001. This combination was reviewed under the FDA's priority review program and was granted fast track designation and expedited review. It is marketed by Novartis as Entresto.

INDICATIONS

Sacubitril/valsartan (SAC/VAL) is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.[1]

DOSAGE

The recommended initial dose is 49/51 mg twice daily.[1] After 2 to 4 weeks, the dose may increase to the target maintenance dose of 97/103 mg twice daily as tolerated. In patients not currently on or previously taking an ARB or angiotensin converting enzyme (ACE) inhibitor, or with severe renal impairment, or moderate hepatic impairment, the starting dose should be reduced to 24/26 mg twice daily. SAC/VAL is available as 24/26 mg, 49/51 mg, and 97/103 mg tablets.

POTENTIAL ADVANTAGES

SAC/VAL provides a new option for heart failure, incorporating two drugs with different mechanisms of action.

POTENTIAL DISADVANTAGES

SAC/VAL is contraindicated in patients who previously experienced angioedema while on ACE inhibitors or ARBs.[1]

COMMENTS

NPs are a family of hormones that maintain sodium and fluid balance.[2] Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are expressed in the atria and ventricles in cases of cardiac hypertrophy and increased stress in the cardiac chamber walls. These peptides cause vasodilation resulting in decreased ventricular preload, systemic vascular resistance, and arterial pressure as well as natriuresis, diuresis, and renin release. NPs are degraded by the neutral endopeptidase neprilysin, and inhibition of neprilysin prolongs the activity of these NPs.

The efficacy of SAC/VAL was established in a randomized, double-blind trial in subjects with symptomatic chronic heart failure with left ejection fraction < 40% (PARADIGM-HF).[1,3] The majority of subjects were on beta-blockers, mineralocorticoid receptor antagonists, and diuretics. After showing no unacceptable side effects at the target dose of the study drug, subjects were randomized to SAC/VAL (97/103 mg; n = 4187) or enalapril (10 mg twice daily; n = 4212). The primary composite endpoint was cardiovascular death or first heart failure hospitalization. The median follow-up time was 27 months, and subjects were treated for up to 4.3 years. The composite endpoint occurred in

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Clinical Briefs

By Louis Kuritzky, MD

How Long Should We Treat with Warfarin for Symptomatic Venous Thromboembolism?

SOURCE: Middeldorp S, Hutten BA. Long-term vs short-term therapy with vitamin K antagonists for symptomatic venous thromboembolism. *JAMA* 2015;314:72-73.

After a symptomatic episode of acute venous thromboembolism, duration of treatment must be individualized. For leg thromboses, the most recent guidelines on antithrombotic therapy by the American College of Chest Physicians (AT9) suggest the decision for duration of warfarin treatment depends on whether the thrombosis is proximal or distal, whether it is provoked (e.g., surgery, trauma) or unprovoked, and whether the level of bleeding risk is low-moderate or high.

Middeldorp and Hutten summarized the evidence by reviewing a meta-analysis of 10 randomized trials (n = 1771) that compared short-term anticoagulation (1-3 months) vs long-term anticoagulation (3-48 months) for the outcome of recurrent venous thrombosis (DVT). Although warfarin was the most commonly employed anticoagulant in this meta-analysis, some trials used acenocoumarol, fluindione, or dicoumarol. For rate of recurrent DVT, no clinical trial indicated superior outcomes for short-term treatment.

Overall, long-term anticoagulation was associated with about an 80% reduction in recurrent venous thromboembolic events compared to short-term anticoagulation (30 events/1771 persons vs 155 events/1765 persons, respectively).

Despite the confirmed risk reduction, clinicians must still take baseline bleeding risk into consideration, since the risk-benefit balance shifts as bleeding risk increases. ■

Extending the Window of Anticoagulation After Pulmonary Embolus

SOURCE: Couturaud F, et al. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: The PADIS-PE randomized clinical trial. *JAMA* 2015;314:31-40.

Utilization of anticoagulation in patients who have suffered an unprovoked pulmonary embolus (PE) is a complex issue. The most recent edition of the guidelines for antithrombotic therapy issued by the American College of Chest Physicians (AT9) suggests that after a minimum of 3 months' anticoagulation post-PE, treatment decisions must be individualized based on bleeding risk. If bleeding risk is considered "low-moderate," then indefinite anticoagulant therapy (with periodic reassessment) is suggested. But are there good outcomes data to support such a recommendation?

Couturaud et al performed a double-blind, placebo-controlled trial in 371 PE patients ascertaining risk of recurrent thromboembolism or major bleeding associated with extended anticoagulation. Patients who had already been treated with 6 months of warfarin were randomized to an additional 18 months of warfarin or placebo. Extended anticoagulation reduced recurrent thromboembolism by 85% (3 events vs 25 events). This benefit was counterbalanced by an increased incidence of major bleeding (4 patients in the warfarin group, 1 in the placebo group). There was no between-group difference in mortality.

After the initial 6-month treatment of PE, extended anticoagulation of up to 18 months dramatically reduces risk of recurrence at the expense of more episodes of major bleeding. Based on patient priorities and preferences, treatment will have to be individualized. ■

Stroke Accelerates Long-term Process of Cognitive Decline

SOURCE: Levine DA, et al. Trajectory of cognitive decline after incident stroke. *JAMA* 2015;314:41-51.

It would likely come as no surprise that acute stroke can lower cognitive function. It might, however, come as a surprise that post-stroke incidence of cognitive impairment (that is, onset of cognitive impairment significantly after the period of acute stroke, rather than immediately post-stroke) is higher, and that once cognitive impairments ensue, the rate of further cognitive decline is faster in persons post-stroke than in controls.

These insights emerged from the REGARDS study (Reasons for Geographic and Racial Differences in Stroke, n = 30,239), which collected data on baseline cognitive function in adults > 45 years of age prior to incident stroke. Hence, the impact of stroke on cognition, as well as the impact on longer-term cognitive decline, is measurable within this data set. In this publication, persons with pre-existing cognitive impairment (that is, pre-stroke) were excluded from analysis.

Following an acute stroke, executive function declined significantly — more steeply than in controls; encouragingly, the capacity for new learning post-stroke did not decline.

Stroke is associated not only with acute cognitive decline in the immediate post-stroke period, but also with a more rapid slope of cognitive function decline over the long-term. ■

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21.8% of the SAC/VAL group compared to 26.5% of the enalapril group (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.73-0.87). The proportions of deaths (cardiovascular or heart failure hospitalization prior to death) or heart failure hospitalization were 13.3% for SAC/VAL vs 16.5% for enalapril and 12.8% vs 15.6%, respectively. Rates for all-cause mortality were 17% vs 19.8%, respectively (HR 0.84; 95% CI, 0.76-0.93). SAC/VAL subjects also required fewer hospital stays or emergency department visits for worsening heart failure and intensification of medical treatment for heart failure.[4] Symptomatic hypotension was more frequent with SAC/VAL than enalapril, 14% vs 9.2%, and cough was more frequent with enalapril, 14.3% vs 11.3%.[3] Overall, fewer subjects on SAC/VAL discontinued their study medication, 10.7% vs 12.3% ($P = 0.03$.)[3] Discontinuation due to renal impairment was 0.7% vs 1.4% ($P = 0.002$.) In the run-in period, 12% discontinued their medications at a higher rate in the enalapril group. The wholesale cost for Entresto is $375 for a 30-day supply.

CLINICAL IMPLICATIONS

SAC/VAL combines a first-in-class neprilysin inhibitor with an ARB. The combination demonstrated clinical benefit over enalapril in subjects who experienced heart failure with reduced ejection fraction. The study (PARADIGM-HF) ended early due to clear benefit. Currently, Novartis is recruiting subjects in a clinical trial, evaluating the effect of SAC/VAL on morbidity and mortality in heart failure patients with preserved ejection fraction (PARAGON-HF). ■

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CME QUESTIONS

1. **Spice intake has been associated with reduced mortality from all of these causes *except*:**
   a. cancer.
   b. ischemic heart disease.
   c. respiratory disease.
   d. infections.

2. **A higher frequency of premature ventricular contraction was associated with:**
   a. a decrease in left ventricular ejection fraction.
   b. no effect on incident congestive heart failure.
   c. no effect on mortality.
   d. all of the above.

3. **Which of the following is correct with regard to patients with uncomplicated acute appendicitis treated with antibiotics alone?**
   a. The majority ultimately required appendectomy.
   b. Their overall complication rates were greater than in those who immediately underwent appendectomy.
   c. Among those who ultimately underwent appendectomy, there was a lower surgical complication rate than among those with immediate appendectomy.
   d. Their pain scores and length of sick leave were each higher than in those who underwent immediate appendectomy.

[IN FUTURE ISSUES]

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Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

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

Is There Complete AV Block?

The simultaneously-recorded 3-lead rhythm strip in the figure was obtained from a 75-year-old woman who presented to the emergency department with syncope. She was diagnosed as being in complete (third-degree) AV block. Do you agree with this interpretation?

If all you saw were the first five beats on this tracing, would you then diagnose complete AV block?

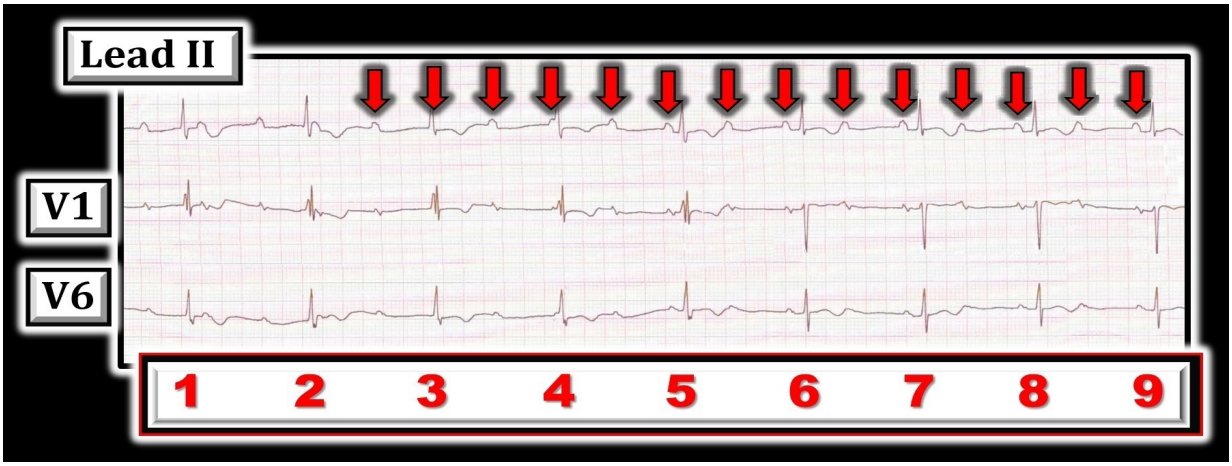

Figure: 3-lead rhythm strip from a 75-year-old woman with syncope. Is there complete AV block? Red arrows in lead II highlight atrial activity.

Interpretation: The advantage of viewing an arrhythmia in several simultaneously recorded leads is that it provides more than a single vantage point. For example, atrial activity is best seen in lead II of this figure, but a change in QRS morphology is best appreciated by QRS appearance in lead V1. We highlight the following features in our interpretation:

- Regular atrial activity is seen throughout this tracing at a rate of about 100/minute (red arrows in lead II).
- QRS morphology changes after the first five beats. While best seen in lead V1, a look at simultaneously recorded leads II and V6 confirms beyond doubt that QRS morphology is different for the last four beats on the tracing. That said, the QRS is no more than minimally widened for the first five beats that probably represent an escape focus arising from below the AV node, but still within the conduction system (most likely from the bundle branch system).
- *P* waves "march through" the QRS (with continually varying PR intervals) for the first five beats in the tracing. None of the *P* waves preceding the first five QRS complexes are conducting to the ventricles. Therefore, there is AV dissociation during the initial part of this tracing. However, the degree of AV block cannot (by definition) be complete, because a constant and normal PR interval is seen to precede the last four beats on the tracing. Every other *P* wave conducts during these last four beats, so that there is second-degree, 2:1 AV block for beats six through nine.

Conclusion: It turns out this patient did receive a permanent pacemaker for her high-grade, second-degree AV block. Nevertheless, this case is illustrative of a number of important diagnostic points. The reason we cannot make the diagnosis of complete AV block from the first five beats on the tracing is that despite AV dissociation, this initial period of monitoring is simply too short. *P* waves don't occur at all points in the cardiac cycle, so they never have full opportunity to conduct, yet fail to do so. In fact, when a strategically placed *P* wave with a PR interval of 0.19 second occurs, sinus conduction (albeit with 2:1 AV block) occurs. Additional findings in support of conduction during the latter part of this tracing include: 1) recognition that beat number six occurs slightly early, and 2) that this earlier-than-anticipated sixth beat manifests a different (slightly narrower) QRS morphology than was seen during the AV dissociation present during the first five beats.

NOTE: Further discussion of this tracing (with laddergram illustration) is available on an ECG video found at this site: ***http://tinyurl.com/KG-Video-9***.