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Internal Medicine

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ABSTRACT & COMMENTARY

Treating Hypertension Without Drugs

By Joseph E. Scherger, MD, MPH

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

SYNOPSIS: High flavanol intake was associated with lower blood pressure in men and women comparable to what is seen with a Mediterranean diet or moderate salt restriction.

SOURCE: Ottaviani JI, Britten A, Lucarelli D, et al. Biomarker-estimated flavan-3-ol intake is associated with lower blood pressure in cross-sectional analysis in EPIC Norfolk. *Sci Rep* 2020;10:17964.

Investigators from Cambridge, UK, studied data from 25,618 participants in the European Prospective Investigation into Cancer (EPIC) trial (Norfolk cohort). They examined an association between diet and blood pressure, specifically the effect of regular flavanol intake. The authors observed significantly lower systolic blood pressure in men (1.9 mmHg) and women (2.5 mmHg). Other studies have shown flavanols are bioactive compounds that improve vascular function. The blood pressure reductions were similar to what has been found with adherence to a Mediterranean diet and moderate salt restriction.

■ COMMENTARY

Hypertension is the grandfather of chronic ailments that lead to cardiovascular disease. It remains the top risk factor for stroke, and a leading risk factor for heart disease. About 90% of hypertension is labeled as "essential," meaning there is no secondary cause. It is estimated nearly half of American adults are hypertensive.[1] Why? Do patients with hypertension need to live with this lifelong chronic disease? Are drugs always necessary to control hypertension?

This work by Ottaviani et al and other related investigations I have written about for *Internal Medicine Alert* concerns the role of healthy nutrition in lowering blood pressure (and improving health in other ways). Plants are rich in the antioxidants called flavanols (sometimes spelled flavonols). They are found in many plants, especially berries, citrus fruits, apples, pears, and strawberries.

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This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

In my medical practice, I strive to eliminate hypertension from patients' problem lists, and help wean them off medications. My healthy lifestyle focus for reversing hypertension includes better nutrition, regular exercise, stress reduction, meditation, and restful sleep. Reducing weight and cutting alcohol consumption are especially helpful in lowering blood pressure. Herbert Benson, MD, at Harvard has used meditation in his hypertension clinic since the 1970s.[2]

Medical decisions about hypertension are based on resting blood pressure. Research has shown that home blood pressure readings may be more accurate than in our office, where we do not take the time to create an environment for rest.[3] If a patient records a home blood pressure of 120/80 mmHg, their pulse pressure is 40 mmHg. If their office blood pressure is 160/80 mmHg, I know the high systolic reading is caused by some stress, either mental or physical. We should not be treating stress with blood pressure medications.

Lifestyle modification usually receives "lip service" in most hypertension guidelines. I learned that every medication causes its own disease. The more we can avoid them in patients and teach a healthy lifestyle, the better off our patients will be. ■

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ABSTRACT & COMMENTARY

Rhythm vs. Rate Control for Atrial Fibrillation Patients: The Controversy Continues

By Tim Drake, PharmD, MBA, BCPS

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

SYNOPSIS: Early use of rhythm control in patients with atrial fibrillation and high cardiovascular risk appears to improve cardiovascular outcomes compared to usual care.

SOURCE: Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;383:1305-1316.

Rate control is the preferred method of treatment for most patients with atrial fibrillation.[1] This recommendation is backed by AFFIRM, a study in which researchers compared rate vs. rhythm control and found no difference between the two methods regarding mortality or stroke. Rate control also was tolerated better.[2] Medications used for rhythm control include amiodarone, dofetilide, and sotalol, which can be proarrhythmic.[1] Even with current therapy, patients with atrial fibrillation are at higher risk for cardiovascular events. The composite of stroke, acute coronary syndrome, heart failure, and cardiovascular death continues to occur at a rate of 5% per year in patients with atrial fibrillation.[3] Additionally, newer medications and improved use of cardiac ablation procedures in the 18 years since the publication of the AFFIRM trial warrant a revisit of rate vs. rhythm.[4]

EAST-AFTNET 4 was an investigator-initiated, international, randomized, open-label, parallel-group trial that included patients with atrial fibrillation. Participants had been living with atrial fibrillation and other cardiovascular conditions for less than one year. Subjects received either early rhythm control or standard of care. Early

rhythm control included cardioversion, antiarrhythmic drugs, or cardiac ablation, with the choice of therapy left up to the treating provider. Standard of care included rate control first, with the option to add rhythm control if the patient remained symptomatic with rate control. The first primary outcome was a composite of stroke, hospitalization because of heart failure, acute coronary syndrome, or cardiovascular death. The second primary outcome was the rate of hospitalizations per year.

The trial ended early after an average follow-up of 5.1 years. The authors randomly assigned 2,789 patients to either group. Of those assigned to rhythm control, 8% received ablation, while 86.8% received a rhythm control medication, with flecainide the most prevalent. At two years, the percentage of patients receiving ablation increased to 19.4%. For rate control, beta-blockers were the most popular treatment (85.5%). Each group exhibited about a 90% anticoagulation rate. The first primary composite outcome occurred in 249 rhythm control patients (3.9/100 person-years) and 316 usual care patients (5.0 per 100 person-years) for a hazard ratio of 0.79 (95% CI, 0.66-0.94; $P = 0.005$). Hospitalizations did not differ between the two groups. Serious adverse events related to rhythm control therapy happened in 1.4% of usual care patients compared to 4.9% of rhythm control patients. More than 70% of patients in both groups were asymptomatic at two years. Quality of life, left ventricular function, and cognitive function also were equal in both groups.

The authors concluded early initiation of rhythm control may produce fewer cardiovascular events compared to usual care in patients with atrial fibrillation for less than one year who have additional cardiovascular conditions. This therapy comes at a cost, with more serious adverse events.

■ COMMENTARY

There are two major goals in treating atrial fibrillation: appropriate anticoagulation to prevent stroke, and ventricular rate control to prevent dilated cardiomyopathy.[1] Historically, rhythm control has been used for symptomatic relief. Kirchhof et al uncovered an association between early rhythm control therapy and fewer adverse cardiovascular outcomes, which may boost its use. In contrast to earlier studies, cardiac ablation was included in this study and may have contributed to the favorable results for rhythm control. Instead of trying to decide which is better (rhythm control or rate control), perhaps the better thought process is to realize there are many tools to treat atrial fibrillation. The clinician must choose the right tool that will fit the patient best. Much like a mechanic may switch tools during a job to better suit the situation, a caregiver now has more viable options to help reduce morbidity and mortality associated with atrial fibrillation. ■

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ABSTRACT & COMMENTARY

Rifampin vs. Isoniazid for Latent Tuberculosis

By Richard R. Watkins, MD, MS, FACP, FIDSA, FISAC

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

SYNOPSIS: A health system cost comparison showed that four months of rifampin was safer and less expensive than nine months of isoniazid in high-income countries, medium-income countries, and African countries.

SOURCE: Bastos ML, Campbell JR, Oxlade O, et al. Health system costs of treating latent tuberculosis infection with four months of rifampin versus nine months of isoniazid in different settings. *Ann Intern Med* 2020;173:169-178.

Latent tuberculosis (TB) infects approximately one in four humans and is a major global health concern. Monotherapy with nine months of isoniazid (INH) became the standard therapy for latent TB in the 1960s. Recently, multiple studies have shown that rifamycin-containing regimens are safer, better tolerated, and can be given for four months instead of nine. However, many policymakers require economic analyses before

new treatment regimens are adapted widely. Therefore, Bastos et al compared healthcare and other costs between nine months of INH and four months of rifampin for the treatment of latent TB. The study included adults and children enrolled in two randomized clinical trials. Inclusion criteria were a positive tuberculin skin test or interferon-γ release assay, a clinical or epidemiologic risk factor associated with an increased risk for developing active TB, and a treating physician's recommendation for treatment of latent TB. Participants underwent a baseline evaluation that included a medical visit, chest X-ray, and routine laboratory tests. In the first month, the authors recommended all participants undergo repeat blood tests. Follow-up visits occurred monthly for the first two months, then at least every eight weeks thereafter.

All participants' healthcare use was tabulated, which included all activities related to the initial medical evaluation, study drugs, follow-up visits, and management of adverse events or active tuberculosis. Direct costs were estimated from the perspective of the country's healthcare system. These included Indonesia, Ghana, Benin, Guinea, Australia, Brazil, South Korea, Canada, and Saudi Arabia. The costs were adjusted using local inflation indices and converted to U.S. dollars as of 2017.

There were 6,012 adults and 829 children included in the modified intention-to-treat analysis. The treatment completion rate was 82% for children and 71% for adults. Participants from Africa logged more follow-up visits compared to other sites, while those from the high-income countries underwent more laboratory tests. In the adult population, those who received nine months of INH recorded twice as many follow-up visits and four times the number of laboratory tests as participants who received four months of rifampin.

The total costs among adults who received rifampin were significantly lower than among those who received INH. In high-income countries, the average cost was $549 for rifampin and $725 for INH. In African countries, it was $112 for rifampin and $140 for INH. Furthermore, costs for adverse event care were lower for rifampin in all settings compared to INH. The rifampin regimen also was less expensive in the pediatric population. Notably, in African countries, the 100-mg INH pill is used, which is more expensive than the 300-mg pill and raised costs in the INH group. In a multivariate analysis, the total health system cost for rifampin was $340 cheaper than the INH regimen (95% CI, $330 to $350), a relative savings of 38%.

■ COMMENTARY

The effect of economics on the healthcare system carries important implications for patient care. Strictly speaking, a four-month supply of rifampin costs more than a nine-month supply of INH. However, this is only part of the equation. Multiple studies have shown four months of rifampin is noninferior to nine months of INH for latent TB — and safer, with a greater likelihood that patients will complete the course of therapy. Indeed, the recent CDC guidelines for latent TB recommend four months of rifampin as the primary regimen.[1] The study by Bastos et al provides another important reason to prescribe rifampin over INH: lower overall healthcare system cost. Thus, the higher cost of the pills should not prevent the adoption of four months of rifampin in latent TB programs, especially in resource-limited settings.

There were some limitations to the study. First, the clinical trials required a minimum number of follow-up visits that might be regarded as excessive in real-world settings. However, multiple guidelines recommend monthly follow-up visits for latent TB. Second, the costs were not standardized across the sites, and the investigators had to use some judgment in deciding the true cost in each country. Third, there were few children enrolled from high-income sites, thus reducing the generalizability of the results for the pediatric population in high-income countries. Finally, costs were not estimated from patients' perspectives (e.g., time lost for appointments, travel expenses, and time to refill medication).

Rifampin now carries another advantage over INH for latent TB: cheaper costs. Treating patients with INH for latent TB should be the exception, not the rule. ■

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ABSTRACT & COMMENTARY

When Aortic Stenosis Is Almost Severe: What Happens Next?

By Michael H. Crawford, MD

Professor of Medicine, Associate Chief for Education, Division of Cardiology, University of California, San Francisco

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

SYNOPSIS: A study of patients with normal flow, low gradients, normal left ventricular systolic function but with calculated aortic valve areas < 1.0 cm^2 showed that about half of them progressed to severe aortic stenosis during the 25-month median follow-up period.

SOURCE: Chadha G, Bohbot Y, Lachambre P, et al. Progression of normal flow low gradient "severe" aortic stenosis with preserved left ventricular ejection fraction. *Am J Cardiol* 2020;128:151-158.

Patients with aortic stenosis (AS) who have normal left ventricular (LV) ejection fraction (EF), normal flow (stroke volume index > 35 mL/m^2 measured at the LV outflow tract), a mean pressure gradient lower than 40 mmHg, but a calculated aortic valve area (AVA) of < 1.0 cm^2 often are referred to as normal flow, low gradient, severe AS (NF-LG-SAS). Their management is controversial. Researchers from three academic medical centers in Belgium and France performed a retrospective observational study that included such patients who also had undergone a second follow-up echocardiogram after at least six months between 2005 and 2015.

The authors excluded patients with more than mild aortic or mitral regurgitation and patients who underwent aortic valve replacement (AVR) between the two echocardiographic exams. The resulting study group consisted of 96 patients (mean age, 79 years; 38% men) with a Charlson Comorbidity Index score averaging 3 and a EuroSCORE II averaging 2.01. The median time between the two echoes was 25 months (interquartile range, 15-52 months). As expected, the severity of AS progressed. Mean aortic pressure gradient increased from 28 to 39 mmHg, peak aortic jet velocity increased from 3.46 to 4.01 m/s, and calculated AVA decreased from 0.87 to 0.72 cm^2 (all $P < 0.001$), but there was no significant change in LVEF. During follow-up, 48% of patients exhibited the parameters of SAS, with mean pressure gradients of > 40 mmHg. The authors concluded NF-LG-SAS with preserved LVEF is an intermediate stage between moderate and SAS and requires close follow up.

■ COMMENTARY

Current American guidelines recognize six levels of AS: mild, mild to moderate, moderate, moderate to severe, severe, and very severe. Chadha et al concluded NF-LG-SAS is moderate to severe AS, and they recommended watchful waiting for such patients.

The study population was highly selected, in that it was mainly elderly women, 83% of whom had class I-II symptoms, and the remainder had class III-IV symptoms. One could argue that symptomatic patients with NF-LG-SAS should undergo AVR, unless the symptoms were thought to be caused by something else.

Interestingly, 48% progressed to NF-high gradient-SAS in a median of 25 months, but only 27% underwent AVR after the second echo. There may be several explanations for this, but the authors did not include any reasons. The average EuroSCORE II was only 2 and the Charlson Comorbidity Index score was 3. Many patients should have at least been candidates for TAVR, which was available in Europe during the study period.

Perhaps the most interesting finding was the mortality rate was 32%. Thus, some patients may have died before AVR could be considered or actuated. Could earlier AVR have mitigated this high mortality rate? The results of some prior studies have suggested this, but others have supported the watchful waiting approach. I hate to think that elderly women are treated less aggressively compared to men in Europe. During follow up, 15% of patients progressed to low flow-LG-SAS, and one-third developed reduced LVEF (< 50%). These patients may have benefited from earlier AVR if they could be identified from the start.

Faced with one of these patients, I believe the priority is to be sure the gradient measurement is correct. Unless continuous wave Doppler from many angles is employed, the peak gradient may be underestimated. Despite the fact cardiologists conducted this study in academic centers, there could have been true high gradient patients who were missed. Second, it would be wise in such patients to employ other less-often-performed measures of AS severity to be certain severe AS was not missed. There is considerable literature supporting the use of the extent of calcium in the valve on CT imaging as a measure of severity that is directly associated with outcome. Also, BNP levels have been shown to correlate with outcomes. More sophisticated echo measures, such as global longitudinal strain, could be conducted to

identify those with subtler LV dysfunction. Finally, cautious exercise testing to identify symptoms likely caused by AS can be performed. Patients whose initial echo shows moderate to severe AS require additional scrutiny to be sure true SAS is not missed before embarking on a course of watchful waiting. ■

PHARMACOLOGY UPDATE

Bamlanivimab Injection

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

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

The FDA has issued an emergency use authorization (EUA) for an investigational monoclonal antibody therapy for mild-to-moderate COVID-19.[1] Bamlanivimab (LY-Cov555) is a neutralizing recombinant IgG1 monoclonal antibody that connects to the receptor-binding domain of the spike protein of SARS-CoV-2. The drug blocks attachment and entry of the virus into human cells.[2] Researchers derived the drug using convalescent plasma obtained from a patient with COVID-19.[3]

INDICATIONS

Bamlanivimab should be used in an outpatient setting to treat mild-to-moderate COVID-19 in adults and pediatric COVID-19 patients (age ≥ 12 years and weight at least 40 kg) who are at high risk for developing severe COVID-19 and/or landing in the hospital.[2] This includes patients with a BMI ≥ 35 kg/m^2, age ≥ 65 years, CV disease, diabetes, and COPD. The drug is not authorized for patients who are hospitalized, require oxygen, or those who required an increase in baseline oxygen flow rate while on chronic oxygen therapy for non-COVID-19-related conditions.

DOSAGE

The recommended dose is a single 700-mg shot administered intravenously over 60 minutes as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset. It should be given in a setting where there is immediate access to treatment of severe infusion reaction, such as anaphylaxis.[2] Bamlanivimab is supplied as a 700-mg/20-mL vial.

POTENTIAL ADVANTAGES

Bamlanivimab provides a treatment option for patients with mild-to-moderate disease as drug evaluations continue. Preliminary data suggest the drug may reduce hospitalization or ED visits and lower symptom severity.[3]

POTENTIAL DISADVANTAGES

Bamlanivimab does not appear to be effective for patients hospitalized with COVID-19, those who require oxygen for COVID-19, or for those who need oxygen for non-COVID-19 conditions. The drug may lead to worse clinical outcomes when given to patients hospitalized with COVID-19 who are on high-flow oxygen or mechanical ventilation.[2]

COMMENTS

The EUA was based on an interim analysis of an ongoing randomized, double-blind, placebo-controlled, Phase II study of subjects who were not hospitalized and had mild-to-moderate symptoms.[1,3] Researchers randomized subjects into four groups: bamlanivimab as a single dose (700 mg, 2,800 mg, or 7,000 mg) or placebo (administered within three days after a positive SARS-CoV-2 test.[3] The primary outcome was change from baseline in SARS-CoV-2 viral load at day 11 (± 4 days) as measured by nasopharyngeal swab and reverse transcriptase polymerase chain reaction. Secondary endpoints were hospitalization/ED visit (28 days after treatment), symptom severity, and safety assessment. The most significant findings in the analysis of 465 subjects was the difference in COVID-related hospitalizations between bamlanivimab-treated and placebo-treated patients in those at high risk for disease progression, hospitalization, and ED visits (3% vs. 10%).[1] Overall viral load declined in all groups, with no clear difference at day 11 (although favorability leaned toward bamlanivimab at day 3). Those randomized to bamlanivimab exhibited slightly lower severity of symptoms from day 2 to day 6. A safety assessment did not reveal any significant serious events vs. placebo. No clear differences in primary or secondary endpoints were observed among the different doses of bamlanivimab. More than 850 subjects have received bamlanivimab in clinical trials. There has been one anaphylaxis reaction and one serious infusion-related reaction.[2] A study of the efficacy of dual therapy (bamlanivimab and remdesivir) in hospitalized subjects has ended, with researchers citing that benefit is unlikely.[4]

CLINICAL IMPLICATIONS

Bamlanivimab is the first monoclonal antibody to be granted an EUA for nonhospitalized patients with mild-

to-moderate disease. Preliminary data suggest it may reduce the rate of hospitalization. Regeneron has developed a "cocktail" of two polyclonal antibodies (casirivimab and imdevimab, REGN-COV2) that targets two different sites of SARS-CoV-2. The manufacturer received an EUA on Nov. 21.[5] The most current NIH COVID-19 treatment guidelines state "there are insufficient data to recommend either for or against the use of bamlanivimab for the treatment of outpatients with mild to moderate COVID-19" and that the drug should not be considered the standard of care.[6] The Infectious Diseases Society of America's recently released guidelines conditionally caution against routine use of bamlanivimab.[7] ■

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CME QUESTIONS

1. What nutrient has been found to lower blood pressure?
a. Polyunsaturated fats
b. Flavonols
c. Canola oil
d. Grapeseed extract

2. Rhythm control therapy was shown to reduce cardiovascular outcomes in:
a. patients with long-standing atrial fibrillation previously treated with rate-controlling medications.
b. patients recently diagnosed with atrial fibrillation who also had additional cardiovascular risk factors.
c. otherwise healthy patients who were just diagnosed with atrial fibrillation.
d. patients with atrial fibrillation for more than one year who had failed cardiac conversion.

3. Which is the current CDC-recommended first-line treatment for latent tuberculosis?
a. Daily isoniazid for nine months
b. Daily rifampin plus isoniazid for four months
c. Daily rifampin alone for four months
d. Weekly isoniazid plus rifapentine for three months

4. An observational follow-up study of patients with normal stroke volume and ejection fraction, and calculated aortic valve area < 1.0 cm^2, but low gradients (< 40 mmHg), after two years showed:
a. a high mortality rate.
b. no change in aortic valve gradient.
c. a decline in ejection fraction.
d. no change in calculated valve area.

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.

Internal Medicine [ALERT]

ECG Review

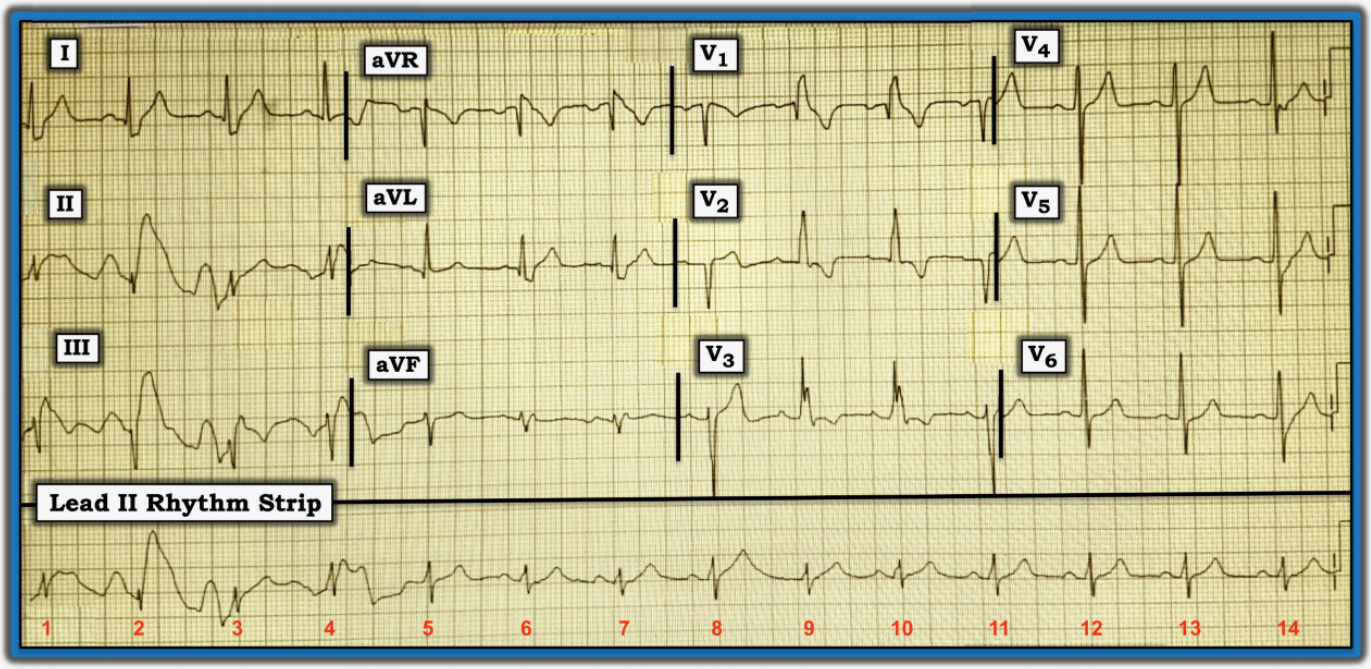
By Ken Grauer, MD

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

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

Is There Bundle Branch Block?

Try to interpret the ECG in the figure below without the benefit of any clinical information. What do you see? Is there bundle branch block (BBB)?



This is a challenging tracing in several respects. In addition to a large amount of artifact and baseline wander, there is obvious change in QRS morphology in certain leads. However, there is hardly any difference in QRS appearance in the long lead rhythm strip at the bottom of the tracing.

It is helpful to begin by determining the underlying rhythm. The upright P wave that appears with a constant PR interval in front of virtually all beats in the long lead II rhythm strip confirms a sinus mechanism.

The clue to what is happening in this tracing lies in lead V1. There are four beats in this lead. The first and fourth complexes in lead V1 are narrow with a negative QRS. The second and third complexes begin with a similar-looking negative deflection, but terminate with a tall and wide R wave. This picture of terminal delay in conduction visible for the second and third complexes in lead V1 is characteristic of right BBB (RBBB). The other characteristic ECG finding for the terminal right-sided delay seen with RBBB is the presence of a wide terminal S wave in lateral leads. This is seen for the first three beats in lead I, as well as for the second and third beats in lead aVL. In contrast, the fourth beat in lead I and the first beat in lead aVL are conducted normally, without any terminal widening (i.e., without any S wave).

The underlying rhythm in this tracing is sinus. There is intermittent RBBB conduction, which is evident in some leads, but not at all obvious in the long lead II rhythm strip.

A subtle advanced point about this tracing is that although the ST-T waves of normally conducted sinus beats (i.e., beats 4, 5, 8, 11, 12, and 13) look unremarkable, there appears to be inappropriate ST segment coving in the two RBBB-conducted beats in leads V2 and V3. Further, the J-point of the ST segment for the three beats conducted with RBBB in lead I is elevated. The patient had positive troponin values.

For more information about and further discussion of this case, please visit: https://bit.ly/38ubOFD.