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Internal Medicine

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

Vol. 39, Issue 5, March 15, 2017
AHCMedia.com

ABSTRACT & COMMENTARY

Role of Statins in Venous Thromboembolism Prevention

By Seema Gupta, MD, MSPH

Clinical Assistant Professor, Department of Family and Community Health, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

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

SYNOPSIS: A large-scale systematic review and meta-analysis found a 15-25% reduction in relative risk for venous thromboembolism in those who used statins vs. those who did not.

SOURCE: Kunutsor SK, Seidu S, Khunti K. Statins and primary prevention of venous thromboembolism: A systematic review and meta-analysis. *Lancet Haematol* 2017;4:e83-e93.

Venous thromboembolism (VTE), which consists of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common public health issue that requires early diagnosis and treatment because of its association with high mortality and morbidity. Although the precise number of people affected by DVT and PE is unknown, up to 900,000 Americans could be affected each year, with a significant number of cases leading to hospitalization, resulting in a high number of fatalities from this preventable illness.[1] The most common inherited etiology for hypercoagulable states include factor V Leiden mutation, prothrombin gene mutation, and defects in protein S, protein C, and antithrombin. Acquired risk factors include a prior thrombotic event, recent major surgery or major medical illness, trauma, immobilization, malignancy, presence of a central venous line, pregnancy, the use of oral contraceptives, myeloproliferative disorders, and antiphospholipid syndrome.

A large body of literature demonstrates that the incidence of VTE can be reduced in the medically ill and surgical populations. Pharmacological prophylaxis may be recommended for patients considered to have an increased risk for VTE and a low risk for

Financial Disclosure: *Internal Medicine Alert's* Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott Diabetes, Actavis, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Cempra, Janssen, Lilly, Merck, 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, MD, is a retained consultant for and on the speakers bureau of, Allergan, Daiichi Sankyo, Lilly, and Lundbeck. Peer Reviewer Gerald Roberts, MD; Executive Editor Leslie Coplin; and 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 twice a month by AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, NC 27518

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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Online only: 1 year (Single user) with *free AMA PRA Category 1 Credits™*: $299

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bleeding, while mechanical compression and/or early ambulation are otherwise recommended for patients considered to be low risk for VTE or high risk for bleeding. Statins are well established as a standard of care for primary and secondary prevention of cardiovascular disease because of their lipid-lowering properties. Statins also are known to exhibit pleiotropic effects on coagulation and inflammation without increasing the risk of bleeding. The effect of statins on DVT prevention was first studied in a 2009 randomized, controlled trial (RCT), which demonstrated that the rate of DVT was decreased significantly in patients treated with rosuvastatin vs. controls.[2] However, a subsequent analysis of pooled studies did not find a significant reduction in VTE with statin use.[3] Since then, there have been a number of newer, more robust studies published on the matter, and there is a need to establish whether the association of statin use with VTE primary prevention exists.

Kunutsor et al conducted a systematic review and meta-analysis of the existing observational cohort studies and RCTs using a predefined protocol. Included were 36 eligible studies published prior to July 18, 2016, that involved more than 3.2 million participants and assessed the association of statin use with VTE in adults, as well as studies that evaluated the effects of statins compared with a placebo or no treatment for VTE outcomes.

Researchers found that in observational studies, there was a 25% reduction in relative risk (RR) for VTE (RR, 0.75; 95% confidence interval [CI], 0.65-0.87; $P < 0.0001$) when statin use was compared with no statin use. In RCTs, there was a 15% reduction in RR for VTE (RR, 0.85; 95% CI, 0.73-0.99; $P = 0.038$) when statin therapy was compared with placebo or no treatment. In the subgroup analyses, significant differences in the effect of statins by type of statin were found, with rosuvastatin demonstrating the lowest risk of VTE compared with other statins (RR, 0.57; 95% CI, 0.42-0.75; $P = 0.015$).

■ COMMENTARY

The findings from this large, well-conducted systematic review and meta-analysis suggests a role for statins in the primary prevention of VTE. The vasoprotective effects of statins may be related to their antithrombotic and anti-inflammatory properties. Increasing evidence suggests that statins modulate the blood coagulation cascade at multiple levels, leading to reduced thrombogenicity and inhibited platelet aggregation while maintaining a beneficial balance between prothrombotic and fibrinolytic processes. Several mechanisms have been proposed for the reduction in thrombosis in patients treated with statins, including decreased tissue factor, plasminogen activator inhibitor-1 decreased platelet aggregation, increased thrombomodulin expression, and increased tissue plasminogen activator expression.[4] There also are decades of data on statins that demonstrate no bleeding side effects, making them a potential adjunctive therapy for VTE.

Interestingly, studies have found that some statins, specifically rosuvastatin, may be more effective than others as a prevention therapy for VTE.[5] Whether VTE reduction is a class effect of statins is uncertain. That raises an important point: Although an extensive body of evidence on the clinical benefit of statins in the occurrence of VTE has been developed, some questions remain unanswered, including the effect of statins on prevention of DVT and PE specifically, the type and dose of statins used, and the benefits of such therapy in patients with normal cholesterol levels. There still exists a need to conduct future intervention research with VTE outcomes prespecified as primary outcomes before guidelines for statin use are expanded to include prevention of VTE. Until then, it is important to keep in mind that the statin we prescribe may play a role in preventing the next thromboembolic event in our patients. ■

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ABSTRACT & COMMENTARY

American Heart Association Recognizes Cardiorespiratory Fitness Should Be Incorporated Into Risk Calculators

By David C. Fiore, MD

Professor of Family Medicine, University of Nevada, Reno

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

SYNOPSIS: Recognizing the many years of data linking cardiorespiratory fitness to cardiovascular and overall mortality, the American Heart Association says cardiorespiratory fitness should be measured or estimated routinely in patients and added to cardiovascular risk calculators.

SOURCE: Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: A case for fitness as a clinical vital sign: A scientific statement from the American Heart Association. *Circulation* 2016;134:e653-e699.

Cardiovascular disease (CVD) remains the leading cause of death and morbidity in the United States.[1] Although it is well established that cardiorespiratory fitness (CRF) is correlated with cardiovascular and all-cause mortality, the Atherosclerotic Cardiovascular Disease (ASCVD) Risk Calculator released jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA) does not include CRF in its calculations. Increasing CRF also has been shown to improve cardiovascular and all-cause mortality. As stated by the researchers, this scientific statement by the AHA attempts to review the "current knowledge related to the association between CRF and health outcomes, increase awareness of the added value of CRF to improve risk prediction, and suggest future directions in research."[2]

The first section of the paper examined CRF and its relation to health outcomes. In their review of studies going back to the 1950s, the authors found a consistent correlation between CRF and health outcomes. They found that CRF was as strong a predictor of mortality as diabetes mellitus, smoking, hypertension, and dyslipidemia. The authors also discovered that CRF levels of < 5 METs were associated with a high risk for mortality, and CRF levels > 8 METs were associated with improved survival. Importantly, the authors found that most of the benefit of increased CRF fitness occurred by increasing from the least fit (< 5 METs) to the not least fit (> 8 METs), and that small increases in CRF (1-2 METs) are associated with 10-30% reductions in mortality. The second section looked at CRF as a predictor of other CVD outcomes and found that CRF is a strong predictor of outcomes such as heart failure, stroke, and surgical outcomes.

The authors then reviewed and discussed the application of CRF to reclassification of cardiovascular risk. They reported that adding CRF to traditional risk factors "significantly improves reclassification of risk for adverse outcomes" and that "traditional risk scores (such as Framingham risk score) are enhanced by adding CRF."

Turning their attention to assessing CRF, the authors reported that cardiopulmonary exercise testing (CPX) is used most frequently in studies, is the ideal testing method, and they believe it is now feasible to do in clinical practice. This typically includes a calculation of peak VO_2, which then can be used to determine METs. Because not all practices will be equipped to perform CPX, the authors reviewed other methods of determining CRF. These methods included maximal and sub-maximal exercise stress testing (EST) as well as estimating CRF from non-exercise equations. They concluded that these non-exercise equations may be "reasonably accurate" but should not replace "objective assessment of CRF, especially in some at-risk patient populations" (not defined).

Looking at the effect of exercise on CRF, the report concluded that "a wide variety of endurance-type physical activity regimens produce clinically significant increases in CRF (i.e., ≥ 1 MET) in most adults." The authors also reported that the less fit a person is, the lower the intensity and/or duration of activity needed

to produce a clinically significant benefit (1 MET).

The authors concluded that "the inclusion of CRF measurement or estimation in routine practice affords clinicians with a vitally important opportunity to improve patient management and, more importantly, patient health."

■ COMMENTARY

Starting when I was in medical school in the 1980s, I've been taught "being fit" lowered one's risk of heart attacks and death. So it's been puzzling that CRF has not been used in estimates of cardiovascular risk, and this AHA statement is very welcome. After counseling patients that they should exercise more, patients sometimes ask how much is needed to lower their risk of a heart attack. I've been unable to answer their question with much confidence. I usually fudge my answer with something like, "We don't have concise estimates of how much you can lower your cardiovascular risks, but if you exercise regularly, it's likely to lower your risk as much as medication." This is consistent with data and conclusions from this report and studies such as the Henry Ford "FIT" project that suggested there is at least a 10% reduction in all-cause mortality for every 1 MET improvement in CRF.[3] Looking at it another way, if someone is very fit (> 9 METs), his or her mortality risk is less than half that of a similar person who is unfit (< 6 METS). It's nice to see that the AHA is finally recognizing this deficit and taking concrete steps to address it. Unfortunately, until risk calculators are developed and validated using CRF as an additional risk factor, clinicians are on their own in figuring out how to use CRF to adjust overall cardiovascular risk. ■

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ABSTRACT & COMMENTARY

Discharge Antibiotic Prescriptions Often Are Inappropriate with Regard to Choice, Dose, Duration

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Seventy percent of discharge antibiotic prescriptions are inappropriate.

SOURCE: Scarpato SJ, Timko DR, Cluzet VC, et al; CDC Prevention Epicenters Program. An evaluation of antibiotic prescribing practices upon hospital discharge. *Infect Control Hosp Epidemiol* 2016 Nov 28:1-3. [Epub ahead of print] PubMed PMID: 27890038.

Scarpato et al retrospectively examined the appropriateness of antibiotics prescribed at discharge from their large, quaternary care, urban teaching hospital that offers a robust antimicrobial stewardship program. During 2014, 7,313 patients received 9,750 discharge antibiotic prescriptions, 86% for oral administration and the remainder to be given parenterally.

Both seven-day and 30-day readmission rates were higher in those with a discharge antibiotic prescription than in the general discharge population: 6.4% and 19.4% vs. 3.7% and 13.8%, respectively. Those patients discharged on a parenteral (intravenous or intramuscular) antibiotic experienced readmission rates that were similar to those of patients prescribed oral antibiotics.

An analysis of a randomly selected subset found that as inpatients, a median of 3.5 days (IQ range, 2-5 days) of antibiotics was received, followed by eight days (IQ range, 6-14 days) as outpatients. Seventy percent of prescribed outpatient antibiotics were judged to be inappropriate regarding choice, dose, or duration, and this was true for 87.7% of surgical patients and 57.6% of medical patients. Thus, among those with a documented infection, the prescribed antibiotic was either too broad spectrum or considered to be insufficiently broad spectrum in 13.7%, and 17% of this group received an incorrect dose. The duration of prescribed administration was too short in 7.3% but was excessive in 55%, and the mean duration of unnecessary antibiotic administration was 3.8 days.

■ COMMENTARY

My colleague, Marisa Holubar, recently developed a new clinical pathway for management of community-acquired pneumonia at Stanford, and as part of the process, examined the baseline duration of antibiotic treatment, which was, as we expected, longer than recommended in national guidelines. A large portion of that excessive duration resulted from the length of continued antibiotics prescribed at discharge. Although we did not investigate it, our assumption was that a major reason was a lack of taking into consideration the days of therapy received before discharge. Thus, the person writing the discharge prescription may be aware that at least five days are currently recommended and proceed to write a prescription for this duration despite the fact that the patient already had received a prescription, e.g., four days of antibiotic therapy as an inpatient. As suggested by Scarpato et al, additional reasons may be lack of knowledge of recommended durations, lack of familiarity with the patient as a result of "hand-offs," and a delay in discharge beyond the anticipated date at the time the prescription was written.

The number of days of unnecessary antibiotic administration has some direct cost consequence, but the more important undesirable effects include increased risk of complications, such as allergic reactions and the development of *Clostridium difficile* infection, as well as the selective pressure exerted on the bacterial ecology with resultant antibiotic resistance.

The problem of inappropriate discharge antibiotic prescribing clearly is one that requires attention and intervention. At the institution where this study was performed, all patients discharged to receive outpatient parenteral antibiotic therapy are followed by a team of infectious disease specialists and pharmacists, but this does not apply to those receiving orally administered antibiotics in the outpatient setting. Interventions suggested by Scarpato et al include medication reconciliation at the time of discharge, prescriber education, and prospective audit and feedback. All will require further engagement for antimicrobial stewardship. ■

PHARMACOLOGY UPDATE

Etelcalcetide Injection (Parsabiv)

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 approved a parenteral, synthetic peptide calcium-sensing receptor agonist (calcimimetic) for the treatment of patients suffering from chronic kidney disease and who are receiving hemodialysis. It is the second calcimimetic to be approved by the FDA for this indication, the first being cinacalcet. These agents increase the sensitivity of the calcium-sensing receptors in the parathyroid gland, resulting in lower parathyroid hormone, serum calcium, and serum potassium levels. Etelcalcetide is marketed as Parsabiv.

INDICATIONS

Etelcalcetide is indicated for secondary hyperparathyroidism in adult patients presenting with chronic kidney disease and who are on hemodialysis.[1]

DOSAGE

The recommended starting dose is 5 mg administered through intravenous bolus injection three times per week at the end of hemodialysis treatment.[1] Maintenance dose is individualized and determined by titration based on parathyroid hormone (PTH) and corrected serum calcium response. The dose range is 2.5-15 mg three times per week. Etelcalcetide is available as 2.5 mg/0.5 mL, 5 mg/mL, and 10 mg/mL single-dose vials.

POTENTIAL ADVANTAGES

Etelcalcetide appears to be more effective than cinacalcet as a higher proportion of patients achieved more than a 50% reduction in PTH level.[2] Etelcalcetide features a long elimination half-life, permitting three-times-per-week dosing, compared to daily oral dosing for cinacalcet.

POTENTIAL DISADVANTAGES

The most common adverse event is related to the extension of the drug's pharmacology: a decrease in blood calcium. This can be severe and can cause paresthesias, myalgias, muscle spasm, seizures, QT prolongation, and ventricular arrhythmias.[1] Heart failure requiring hospitalization has been reported (2% vs. 1% in placebo). Other common adverse events include diarrhea and nausea.

COMMENTS

The efficacy and safety of etelcalcetide were determined in two randomized, double-blind, placebo-controlled, 26-week studies in subjects presenting with moderate to severe secondary hyperparathyroidism with chronic kidney disease.[1,3] The authors of the first study randomized 254 patients to etelcalcetide and 254 to placebo. In the second study, the groups were 255 and 260, respectively. The starting dose was 5 mg three times per week at the end of hemodialysis and titrated every four weeks until week 17 to a maximum dose of 15 mg three times per week to a target PTH level of ≤ 300 pg/mL. Administration was temporarily suspended if there were two consecutive PTH levels < 100 pg/mL, and the dose was not increased if PTH levels were ≤ 300 pg/mL, corrected serum calcium < 8.3 mg/dL, symptomatic hypocalcemia occurred, or at the discretion of the investigator. The primary endpoint was the proportion of subjects with a > 30% reduction in PTH levels from baseline to the efficacy assessment (mean levels for week 20-27, inclusive). The secondary endpoint was the proportion with PTH < 300 pg/mL. In both studies, the primary endpoint was significantly higher, with > 30% reduction with etelcalcetide vs. placebo (77% vs. 11% and 79% vs. 11%). For the secondary endpoint, the values were 52% vs. 6% and 56% vs. 5%. In a 26-week comparative study, etelcalcetide (n = 340) was compared to oral cinacalcet (30 mg daily; n = 343) in a noninferiority design.[3] Although noninferiority was established, with primary endpoint of 30% reduction in PTH, etelcalcetide showed a greater reduction in PTH levels (52.4% vs. 40.2%) from baseline and reduction in certain markers of high-turnover bone diseases. The long-term safety and effectiveness of etelcalcetide remains to be determined.

CLINICAL IMPLICATIONS

Hyperparathyroidism is a common complication of chronic kidney disease. This condition leads to cardiovascular and bone complications.[4] Management ranges from low phosphorus diet, phosphate binders, vitamin D analogs, to calcimimetics. A Cochrane review suggests that cinacalcet therapy may reduce the need for parathyroidectomy in adults with dialysis and elevated PTH but does not improve all-cause or cardiovascular mortality.[5] Etelcalcetide is a potentially more effective calcimimetic agonist, although it requires intravenous administration vs. oral administration of cinacalcet. However, this can be conveniently timed with hemodialysis treatment. The cost of etelcalcetide is not yet available. ■

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CME QUESTIONS

1. **Based on the study by Kunutsor et al, there was a ___ reduction in the risk of venous thromboembolism in those who used statins compared to those who did not use statins.**
   a. 15-25%
   b. 25-35%
   c. 35-50%
   d. 50-60%

2. **Which of the following is true?**
   a. Cardiorespiratory fitness is at least as important in predicting cardiovascular outcomes as traditional risk factors such as hypertension, lipids, and smoking.
   b. Cardiorespiratory fitness can be calculated only using sophisticated equipment that can calculate VO_2 max or VO_2 peak.
   c. Cardiorespiratory fitness has been shown to be modifiable.
   d. Both a and c are true.

Clinical Briefs

By Louis Kuritzky, MD

Comparing Treatments for Peripheral Artery Disease Patients

SOURCE: Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017;376:32-40.

Clopidogrel has demonstrated superiority to aspirin for reducing cardiovascular events in patients with stable vascular disease (i.e., post-myocardial infarction, post-stroke, prevalent peripheral arterial disease). In the CAPRIE trial, patients on clopidogrel experienced an almost 9% lower relative risk of cardiovascular events than patients on aspirin, although the absolute risk reduction was very small (0.5%). At the time of publication of the CAPRIE trial, this presented a dilemma for clinicians, primarily because of cost issues.

Ticagrelor is in the same class of agents as clopidogrel: Both are P2Y12 inhibitors, which lead to reduced platelet aggregation. The success that ticagrelor has achieved in acute coronary syndromes prompted the question of whether ticagrelor might provide greater reduction in cardiovascular events than clopidogrel, since the presence of peripheral arterial disease (whether symptomatic or not) is indicative of coexisting coronary artery disease.

Hiatt et al conducted a randomized, double-blind, placebo-controlled trial of ticagrelor vs. clopidogrel in patients with peripheral arterial disease (n = 13,885). The primary outcome was incident cardiovascular events over 2.5 years.

There was no statistically significant difference in cardiovascular outcomes between the two agents. The additional expense of ticagrelor, plus the fact that it is administered b.i.d in contrast to the q.d. dosing of clopidogrel, suggest that clopidogrel should remain the preferred agent. ■

Is the Intestinal Microbiome the Culprit in Obesity?

SOURCE: Komaroff AL. The microbiome and risk for obesity and diabetes. *JAMA* 2017;317:355-356.

Apparently, the gut bacteria — currently called the microbiome — are much more than simple innocent bystanders. There are two primary families of intestinal microbiota: *Bacteroidetes* and *Firmicutes*, which comprise approximately 90% of all gut bacteria. Recently, it has been appreciated that the microbiome actually generates proteins, hormones, neurotransmitters, and inflammatory molecules. These products of the microbiome may enter the circulation and produce far-reaching effects.

For instance, obese persons are populated with greater numbers of *Firmicutes*, which are more efficient in providing energy sources than *Bacteroidetes*. Confirming the causal role of this relationship, transplantation of gut microbiota from obese mice promptly converts lean mice into obese ones. Equally remarkable, and much more hopeful, is the observation that transplantation of microbiota from lean mice into obese ones produces a favorable effect on weight.

The story is complicated even further by the observation that the microbiome is capable of remodeling: When obese persons consume weight-reducing diets, the disproportion of *Firmicutes* declines, and it resumes when excess calories are again introduced. We are only beginning to understand the magnitude of the role the microbiome plays in health and disease. ■

The Dubious Benefits of Urinalysis in Asymptomatic Patients

SOURCE: Bush LM, Vazquez-Pertejo MT. The unintended deleterious consequences of the 'routine' urinalysis. *Am J Med* 2017;130:3-4.

The only population in which treatment of asymptomatic bacteriuria might be beneficial appears to be pregnant women, and even that widely held belief has been challenged recently. Part of the problem of addressing asymptomatic bacteriuria is that often we are dealing with results of a test we may not have thought was really pertinent to the patients well-being (or lack thereof) in the first place. That is, so-called "routine" urinalysis — usually by urine dipstick — may be part of standard protocol for patients presenting with no symptoms even remotely referable to the genitourinary tract.

Were asymptomatic bacteriuria rare, perhaps the problem would not be so vexing. On the contrary, the prevalence in long-term care facility residents may be as high as 25-50% in women and 15-40% in men. When presented with such abnormal results, clinicians often are tempted to treat, hoping to avoid more serious consequences. However, clinical trial data do not demonstrate achieved benefit.

Both the Infectious Diseases Society of America and the American Board of Internal Medicine advise against treatment of asymptomatic bacteriuria in non-pregnant adults. Clinicians would be wise to heed such advice, and perhaps even better, be more selective about seeking urine testing only when clinically pertinent. ■

Internal Medicine [ALERT]

ECG Review

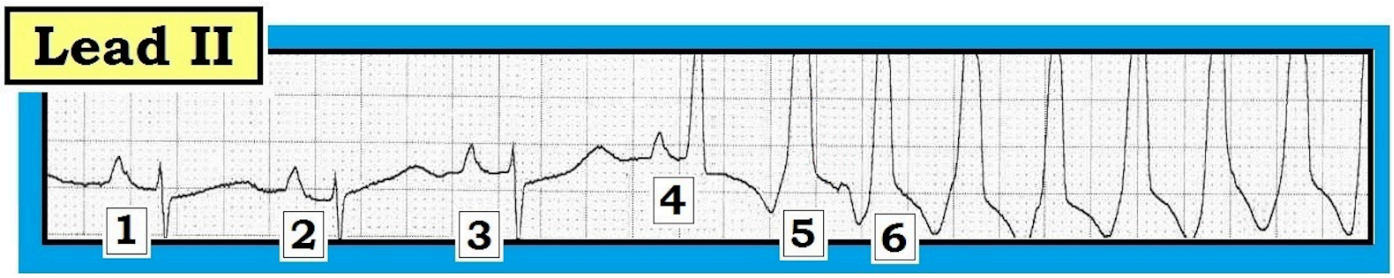
By Ken Grauer, MD

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.

Are There Definitive Clues?

The lead II rhythm strip shown in the figure below begins with three sinus-conducted beats. There follows a run of a wide complex tachycardia (WCT). How certain are you that the run of WCT that begins with beat #4 is ventricular tachycardia (VT)?



The first three beats in the figure are sinus-conducted. The PR interval is upper normal at 0.20 seconds. The P-P interval changes slightly, which means there is underlying sinus arrhythmia. QRS morphology then abruptly changes beginning with beat #4. The QRS widens and is oppositely directed (all positive) compared to the narrow rS complexes of the first three beats. There is no reason for aberrant conduction to occur beginning with beat #4 because beat #4 occurs late in the cycle, at a time by which conduction properties that lead to aberrancy should have resolved. Instead, we can say with 100% certainty that the run of wide beats beginning with beat #4 is VT.

The first principle is that abrupt onset of a regular (or at least fairly regular) wide rhythm of different morphology than sinus-conducted beats predicts VT with > 90% likelihood. Consideration of clinical details (i.e., history of underlying heart disease and/or prior documented VT episodes), together with morphologic ECG features, often can increase certainty of our diagnosis beyond this level.

Beat #4 is a fusion beat. Note that the PR interval preceding beat #4 is shorter than the PR interval preceding each of the three sinus-conducted beats. This means that something else must have happened to produce the oppositely directed upright QRS complex of beat #4 because the on-time sinus P wave preceding beat #4 simply did not have enough time to complete its conduction through the ventricles.

Fusion beats manifest QRS and ST-T wave morphology intermediate between the QRS and ST-T wave morphology of sinus-conducted beats and ventricular beats. Depending on how deep in the ventricles the sinus P wave is able to penetrate, the resulting QRS and ST-T wave will look more like sinus beats or ventricular beats. Beat #4 is upright like the wide run that follows, but this beat is not quite as wide, nor is its negative T wave as deep because there is fusion (simultaneous occurrence) of supraventricular and ventricular activation.

AV dissociation also appears on this tracing, at least at the beginning of the run of wide beats. The P wave preceding beat #4 is on time. Note that another on-time P wave appears to notch the ST-T wave just after beat #5. But since these P waves do not conduct normally, there is AV dissociation. The abrupt onset of a different wide run with fusion beats and AV dissociation provides indisputable proof that the rhythm in the Figure is VT.

For more on this case, please visit: http://bit.ly/2mbW9Ah.