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Internal Medicine

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ABSTRACT & COMMENTARY

Cholesterol Levels and Predicted Survival Rates Among Elderly Women

By David Fiore, MD

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

SYNOPSIS: In this retrospective review of data from the Women's Health Initiative, researchers found that neither low levels of high-density lipoprotein nor high levels of low-density lipoprotein were associated with predicted survival in older women. This finding is consistent with other studies of cholesterol and mortality in the elderly.

SOURCE: Maihofer AX, Shadyab AH, Wild RA, LaCroix AZ. Associations between serum levels of cholesterol and survival to age 90 in postmenopausal women. *J Am Geriatr Soc* 2020;68:288-296.

There is evidence showing that high levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) cholesterol are associated with an increased risk for cardiovascular events and death among the general population. Further, research has shown that treatment with statins can lower this risk in the general population. However, it is unclear if these relationships hold true in the elderly. The 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease does not address lipids or statin therapy in patients older than age 75 years.[1] The authors of other reviews have found conflicting evidence of the benefit of treating dyslipidemia in the elderly, especially in primary prevention. A 2014 meta-analysis revealed a benefit in treatment for secondary prevention and a trend toward a benefit for primary prevention in the elderly.[2,3]

More recent studies have cast doubt on the clinical significance of dyslipidemia in the elderly and on the benefits of treatment. In 2016, Ravnskov et al published a review of 19 cohort studies with 68,094 subjects older than age 60 years. They found an inverse relationship between LDL cholesterol and mortality.[4] In 2019, Nanna et al used individual level data from the National Institutes of Health Pooled Cohorts

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(which included Framingham, Framingham Offspring Study, Multi-Ethnic Study of Atherosclerosis, and Cardiovascular Health Study).[5] Looking at data from 2,667 adults with a median age of 78 and median LDL cholesterol of 117 mg/dL, the authors found no difference in event rates (stroke, myocardial infarction, or cardiovascular death) in those with or without hyperlipidemia. This lack of correlation held regardless of risk factors.

Maihofer et al used data from the Women's Health Initiative (WHI) to examine the relationship between LDL and HDL and survival status and self-reported mobility. The WHI started in 1993 at 40 clinical centers across the United States, with 161,808 participants between the ages of 50 and 79 years. In 2005, 115,400 surviving participants re-enrolled for an extension study. In 2010, 93,540 re-enrolled for another extension. A total of 27,940 participants had lipid assays; of those, 4,838 were selected for the current analysis based on their ability to reach their 90th birthday by Aug. 31, 2016. Of these, another 1,371 were excluded due to vascular or cardiovascular disease, cancer, or statin use, leaving 3,567 for primary analysis, with 117 of these lost to follow-up. Mobility status was determined by mailed surveys using the 36-Item Short Form Health Survey (SF-36).

Women with higher LDL levels were more likely to be alcohol drinkers; white; and to have higher triglyceride, blood pressure, and total cholesterol (but lower HDL) levels. They were less likely to be college educated or have a history of diabetes that required treatment.

Women with higher HDL levels were more likely to have lower systolic blood pressure readings, to have a lower body mass index, to be African American, and to be college educated. Further, these subjects reported very good or excellent self-rated health, engaged in more physical activity, and recorded higher total cholesterol (but lower LDL and triglyceride) levels.

After adjusting for age and race/ethnicity, higher HDL levels were significantly associated with higher odds of living to age 90 years vs. the lowest quartile (odds ratio, 1.24; 95% confidence interval, 1.03-1.50). However, after the authors adjusted for lifestyle and medical factors, the association was attenuated and no longer statistically significant. Higher HDL levels also correlated with intact mobility to age 90, but was attenuated when the authors adjusted for lifestyle factors (but not by medical factors).

■ COMMENTARY

There were some important limitations to this (and similar prior) studies. First, remember we are talking about primary prevention. If an elderly patient already has cardiovascular disease, the current recommendations (aggressive treatment of dyslipidemia) still hold. Second, the authors used data from the WHI, which means this information was only for elderly women. There also were significant confounders, such as race, education, and diabetes, for which the researches tried to account, but this always makes it more difficult to interpret the significance of the results. Third, and what I struggle with in practice, is how to manage the elderly or very elderly patient who has been on a statin for primary prevention for years and has never experienced a cardiovascular disease event. Should we stop or continue the statin? Since there does not appear to be good evidence either way, shared decision-making, with an honest discussion of what we do not know, may be the best approach. ■

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ABSTRACT & COMMENTARY

Low TMAO for a Healthy Heart

By Joseph E. Scherger, MD, MPH

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

SYNOPSIS: The gut microbial metabolite trimethylamine N-oxide (TMAO) is a predictor of coronary artery disease (CAD). TMAO forms mainly through eating red meat and other animal products, such as eggs and dairy. Long-term changes in TMAO is a predictor of CAD and speaks to the benefits of a plant-based diet to prevent heart disease.

SOURCE: Heianza Y, Ma W, DiDonato JA, et al. Long-term changes in gut microbial metabolite trimethylamine N-oxide and coronary heart risk. *J Am Coll Cardiol* 2020;75:763-772.

Heianza et al conducted the first longitudinal, prospective study of heart risk from elevated trimethylamine N-oxide (TMAO) levels. The authors used the Nurses' Health Study to obtain baseline TMAO levels, and followed 760 healthy women from 1989-1990 to 2000-2002. The increase in coronary heart disease (CAD) had a linear relationship with TMAO levels. For every one standard deviation increase in TMAO levels, there was a 33% increase in CAD risk. Women with the largest increases in TMAO levels had a 67% higher risk for CAD. TMAO is formed when gut bacteria metabolize nutrients such as choline, L-carnitine, and phosphatidylcholine found in red meat, egg yolk, and high-fat dairy products. This produces trimethylamine, which is converted into TMAO in the liver. TMAO affects lipid metabolites in the liver in such a way as to facilitate dyslipidemia. In high amounts, TMAO increases the risk for myocardial infarction, stroke, and all-cause death.

■ COMMENTARY

Advocates of a whole food, plant-based diet use research data surrounding TMAO to argue against the consumption of animal food products, especially red meat, but also eggs and dairy. The data are compelling enough to argue for limiting such exposure. The two healthiest diets by research data are a version of the Mediterranean diet and a whole food, plant-based diet. The Mediterranean diet emphasizes plants, and the meat content is only about 10% of the whole.[1] Most seafood is not a source of TMAO. This would speak to a pescatarian diet.[2] Primary care physicians should be aware of TMAO and its cardiac disease risks. This is part of recommending healthy diets. TMAO can be measured in the blood, and most commercial labs offer the test. I do not conduct this testing due to dietary fluctuations, but I do use information about TMAO to recommend healthy dietary choices that include limiting the consumption of animal products. ■

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ABSTRACT & COMMENTARY

Home Oral Factor Xa Inhibitor Treatment for Pulmonary Embolism

By Michael Crawford, MD

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

SYNOPSIS: Low-risk pulmonary embolus patients discharged in < 48 hours on rivaroxaban recorded a nominal three-month rate of recurrent emboli or major bleeding, suggesting such patients do not need to be hospitalized for treatment of pulmonary emboli.

SOURCE: Barco S, Schmidtmann I, Ageno W, et al. Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: An international multicenter single-arm clinical trial. *Eur Heart J* 2020;41:509-518.

Prior studies of using vitamin K antagonists to treat low-risk pulmonary embolism (PE) patients at home have been controversial due to study design limitations, including the definition of low risk. Recently, direct oral anticoagulants (DOACs) have been used successfully to treat acute PE patients.

Barco et al conducted a multicenter, single-arm study of early discharge and ambulatory treatment with rivaroxaban in low-risk PE patients to determine its efficacy and safety (HOT-PE trial). The identification of low-risk PE patients employed the European Society of Cardiology clinical criteria, plus the presence of normal right ventricular (RV) size and function and the absence of mobile thrombi in the right heart on echocardiograms. Treatment with heparin or an oral anticoagulant was allowed before enrollment. Researchers cut off prior treatment, and started subjects on rivaroxaban less than two hours later. The doses of rivaroxaban followed the manufacturer's recommendations. Patients were discharged within 48 hours of the diagnosis of PE, and treatment continued for three months. The primary efficacy outcome was recurrent PE or PE-related death. The safety outcomes were major bleeding, clinically relevant nonmajor bleeding, and serious adverse events.

An interim analysis was conducted after 525 patients had completed their three-month visit to determine if premature study discontinuation was warranted for clear efficacy or harm. In 49 centers in seven countries, 2,854 patients with PE were screened and 525 were enrolled (2,329 were excluded). The enrolled patients' average age was 57 years, and 46% were women. The median length of initial hospitalization was 37 hours. Only three of the 525 enrolled patients experienced the primary outcome of recurrent nonfatal PE, so the study ended prematurely based on prespecified statistical criteria. The primary safety outcome of major bleeding occurred in six patients, clinically significant bleeding in 31, and serious adverse events in 58. Two patients died of cancer. The authors concluded that selected low-risk PE patients can be treated effectively and safely with early discharge on rivaroxaban therapy.

■ COMMENTARY

Since the efficacy and safety of DOAC vs. warfarin in outpatients with deep vein thrombosis (DVT) has been demonstrated, the investigators in HOT-PE believed it was unnecessary to include a conventionally treated control group. Exclusion criteria were straightforward: serious comorbidities, another condition requiring hospitalization, and a social environment not conducive to ambulatory anticoagulation management. In fact, 21% of patients recorded a simplified pulmonary embolism severity index (sPESI) score of ≥ 1 (a score of 0 is low risk), but the authors excluded patients with right heart dysfunction and thrombi, which clinical indices such as sPESI do not consider. Also, in their multivariate analysis, neither age nor a history of cancer (both in sPESI) affected the results.

The study ended early at 50% of the planned enrollment because the primary endpoint of recurrent PE was 0.6%, so the null hypothesis was rejected early. The authors of similar studies with warfarin observed PE recurrence rates of 0.6-2.0%. The safety outcome of major bleeding was 1.2% in the Barco et al study and 0.7-1.8% in prior trials with warfarin. In previous trials of rivaroxaban in DVT, the major bleeding rates were 0.5-2.0%. Thus, efficacy and safety are similar to PE trials with warfarin and DVT studies with DOACs.

The decision to discharge a patient early after PE is important because PE can be fatal. In this study, three patients experienced recurrent PE, and there were no PE-related deaths over the three months of the study. These results are compelling for triaging more patients to ambulatory care, but how many are going to meet the inclusion criteria for early discharge? In this trial, it was 20% — significant enough to reduce costs and make some patients happy. Of course, it does require initial hospitalization and treatment with heparin, enoxaparin, or other anticoagulants, along with an echocardiogram to cull the highest-risk patients with right ventricular dysfunction or mobile thrombi. However, this would be standard protocol for most other hospitalized patients. The next step is identifying low-risk patients at the point of first encounter with immediate triage of low-risk patients to ambulatory care. The key to this step is the availability of echocardiography. ■

ABSTRACT & COMMENTARY

Diagnostic Criteria for Small Fiber Neuropathy

By Mary L. Vo, MD, PharmD

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Dr. Vo reports she is an advisory board member for CSL Behring, is a consultant and advisory board member for Alexion Pharmaceuticals, and receives grant/research support from Takeda Pharmaceuticals.

SYNOPSIS: Multiple clinical tools have emerged to assess small fiber nerve dysfunction, but validated diagnostic criteria are needed to optimize diagnostic sensitivity, support clinical management, and facilitate patient selection for clinical trials.

SOURCE: Devigili G, Rinaldo S, Lombardi R, et al. Diagnostic criteria for small fibre neuropathy in clinical practice and research. *Brain* 2019;142:3728-3736.

Small fiber neuropathy (SFN) is a heterogenous condition characterized by impairment of Aδ and C nociceptive fibers involved in sensory perception to pain, temperature, and itch in addition to regulation of autonomic functions. Although various phenotypes have been described, a classic presentation is burning pain and paresthesias affecting the distal extremities. Given the clinical heterogeneity, symptom reporting alone is not reliable as a screening tool.[1] Clinical examination findings can include lower temperature and pain perception in a distal gradient, although the exam can be normal in some patients. Nerve conduction studies are important to identify patients with large-fiber neuropathy but are normal in patients with isolated small fiber dysfunction.

Intraepidermal nerve fiber density (IENFD) and quantitative sensory testing (QST) are the most sensitive and commonly used diagnostic tools for SFN. IENFD obtained by skin biopsy of the distal leg is a reliable and widely used confirmatory test for SFN. Its diagnostic accuracy has been improved by availability of updated normative data.[2] QST is designed to assess Aδ, Aβ, and C fiber sensory function and involves sequential application of thermal and mechanical stimuli to multiple standardized sites in the extremities while evaluating for abnormal sensation, allodynia, hyperalgesia, and aftersensation compared to published reference values.[3] Thermoregulatory, autonomic, somatic, and sudomotor function tests have been developed to complement the clinical evaluation, but generally are limited to specialized centers. Validated diagnostic criteria combining clinical evaluation and diagnostic tools are needed to optimize diagnostic sensitivity, support clinical management, and facilitate patient selection for clinical trials.

Devigili et al compared the sensitivity of the Besta criteria[4] and the NEURODIAB[5] criteria for definite SFN. The Besta criteria require two objective clinical signs of small fiber impairment plus abnormal QST or IENFD. In contrast, the NEURODIAB criteria require the presence of a single clinical sign, a normal sural nerve conduction study, and either abnormal QST or IEFND. In the reappraisal portion of the study, the authors assessed historical clinical, IENFD, and QST data from 150 patients included in the original Besta study[4] using updated IENFD reference values. Results showed a high level of agreement between the Besta and NEURODIAB criteria for definite SFN (area under the curve 0.98; 100% sensitivity; 98.5% specificity). The prospective validation study included 352 new and follow-up patients with suspected sensory neuropathy evaluated at a single Italian neurological center from January 2009 to September 2017. Symptom inventory questionnaires, detailed neurological exam, electrophysiologic testing, IENFD, and QST were obtained for all patients. A statistical analysis was performed using unpaired t-test and Mann-Whitney test to compare normally and non-normally distributed values, respectively. Paired t-test and Pearson R2 coefficient test were used to compare clinical exam to QST.

A total of 149 of 187 symptomatic patients without clinical or electrodiagnostic evidence of large fiber neuropathy satisfied the Besta criteria for definite SFN. An additional 34 patients were designated as possible SFN based on symptom reporting, but had normal clinical evaluation, IENFD, and QST testing. Four patients who had symptoms and abnormal QST also were deemed possible SFN. The NEURODIAB criteria was highly concordant with the Besta criteria (sensitivity 94.6%; specificity 99%), supporting the validity and reliability of the clinical assessment. Moreover, IENFD had higher sensitivity, specificity, and diagnostic efficacy compared to QST. At the time of follow-up, 29 of 98 patients with definite SFN were reclassified as having large fiber neuropathy or sensory neuronopathy. Eight patients with definite SFN based on abnormal QST and IENFD developed clinical exam abnormalities at the time of follow-up. Nineteen of 38 patients with possible SFN based on symptoms alone reported complete resolution and had a normal examination. Four patients with possible SFN based solely on abnormal QST also had normal clinical examinations and IENFD at follow-up. The combination of clinical examination, IENFD, and QST provides an accurate and reliable screen for SFN. Compared to QST, IENFD showed higher sensitivity, specificity, and diagnostic efficiency.

■ COMMENTARY

The high concordance between Besta and NEURODIAB highlight the reliability of a focused clinical exam as a screening tool for patients presenting with classical symptoms of SFN, particularly when at least two clinical signs are present. IENFD remains the most sensitive confirmatory test available for diagnosis of SFN. QST is a valid technique that can further increase diagnostic sensitivity for clinical research, but its clinical utility is limited by the technical and time-consuming nature of the test. The high reliability and sensitivity of the combined profile of clinical examination, QST, and IENFD would improve patient selection for clinical trials and serve as reliable outcome measures for future disease-modifying therapies. ■

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PHARMACOLOGY UPDATE

Rimegepant Orally Disintegrating Tablet (Nurtec ODT)

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 Food and Drug Administration has approved the second oral, non-peptide, small molecule, calcitonin gene-related peptide (CGRP) receptor antagonist, following ubrogepant, for acute migraine. Rimegepant is the first quick-dissolving tablet approved for this indication. It received a priority review and is marketed as Nurtec ODT.

INDICATIONS

Rimegepant should be prescribed to treat acute migraine with or without aura in adults.[1]

DOSAGE

The recommended dose is 75 mg placed on or under the tongue as needed.[1] No water is needed. The maximum dose is one tablet in a 24-hour period. The safety of treating more than 15 migraines that occur in a 30-day period has not been established.[1] Rimegepant is available as 75 mg orally disintegrating tablets (ODT).

POTENTIAL ADVANTAGES

Rimegepant is a quick-dissolving tablet that does not require water for administration. It may onset faster vs. ubrogepant. Rimegepant also has a long elimination half-life (approximately 11 hours) vs. five to seven hours for ubrogepant.[1,2] This may contribute to a longer duration of action.

POTENTIAL DISADVANTAGES

Rimegepant is a substrate of CYP3A4 as well as transporters P-gp and breast cancer-resistant protein (BCRP); thus, avoid using with strong CYP3A4 inhibitors, strong and moderate CYP3A4 inducers, and inhibitors of P-gp or BCRP.[1]

COMMENTS

The efficacy of rimegepant was evaluated in a randomized, double-blind, placebo-controlled trial.[1,3] Adult subjects with at least a one-year history of migraine, with or without aura, were randomized to rimegepant 75 mg (n = 732) or placebo (n = 734). Subjects were instructed to treat a migraine of moderate to severe headache pain intensity. The coprimary endpoints were percent with freedom from pain and freedom from the most bothersome symptoms (MBS), such as nausea, phonophobia, or photophobia, at two hours postdose. Pain relief was defined as a reduction in migraine pain from moderate or severe severity to mild or none.

Percent responders pain free at two hours were 21.2% for rimegepant vs. 10.9% for placebo. Response for MBS was 35.1% vs. 26.8%, respectively. A series of secondary endpoints included assessed onset of action and durability of effect.[2] A higher proportion showed the ability to function normally at 60 minutes postdose (22.3% vs. 15.8%), pain relief at 90 minutes (49.6% vs. 37.2%), sustained pain relief two to 24 hours (47.8% vs. 27.7%), sustained pain relief two to 48 hours postdose (42.2% vs. 25.2%), and use of rescue medication within 24 hours (14.2% vs. 29.2%). Rimegepant appears to be well tolerated. Common adverse events related to treatment were 7% vs. 5% for placebo. These include nausea, urinary tract infection, and dizziness. The most common adverse reaction reported in a long-term, open-label study (n = 1,798) with up to one year of intermittent use was nausea (2% vs. 0.4% for placebo).[1]

CLINICAL IMPLICATIONS

The American Headache Society recommends triptans, ergotamine derivatives, and nonsteroidal anti-inflammatory drugs (NSAIDs) to treat acute migraines.[4] Triptans are first-line treatment, but they are not suitable for patients with vascular risk factors (e.g., ischemic or vasospastic coronary artery disease). In addition, effectiveness and tolerability vary between triptans and individual patients.[5] So far, cardiovascular (CV) adverse events have not emerged

in clinical trials of rimegepant or ubrogepant, and specific warnings are not part of the current prescribing information. However, patients with CV contraindications were not included in the clinical trials. There are no comparative studies comparing the two oral CGRP inhibitors. Comparing the respective placebo-control studies, the coprimary endpoint responses at two hours postdose appear similar, but the relative time courses of response suggested rimegepant may onset faster and possibly last longer.[1-3] Other recent approvals include lasmiditan (a serotonin 1F receptor agonist), ubrogepant, and now rimegepant, all of which may be options for patients who have contraindications to triptans or who have failed to respond to or are intolerant of oral triptans (although these subgroups have not been studied). A recently released report by the Institute for Clinical and Economic Review concluded these three new therapies appear to be less effective overall than triptans.[6] They are significantly more expensive, particularly compared to generic triptans. The cost of rimegepant is expected to be $850 per eight-tablet pack, or just over $100 per tablet. ■

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CME QUESTIONS

1. **In the Heianza et al study, for every one standard deviation increase in trimethylamine N-oxide levels, the risk for coronary artery disease increased:**
   a. 50%.
   b. 75%.
   c. 33%.
   d. 20%.

2. **Which tool enhances the clinical identification of low-risk pulmonary embolism patients for ambulatory care who are taking a direct oral anticoagulant?**
   a. CT angiography
   b. Ventilation perfusion scan
   c. Electrocardiogram
   d. Echocardiography

3. **According to the Maihofer et al study, which statement is true?**
   a. Elevated low-density lipoprotein (LDL) is not associated with increased cardiovascular risks.
   b. Elevated LDL in elderly men is cardio-protective.
   c. Elevated LDL in elderly women with prior cardiac events is not associated with increased cardiovascular risks.
   d. Elevated LDL in elderly women without heart disease is not associated with increased cardiovascular risk.

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

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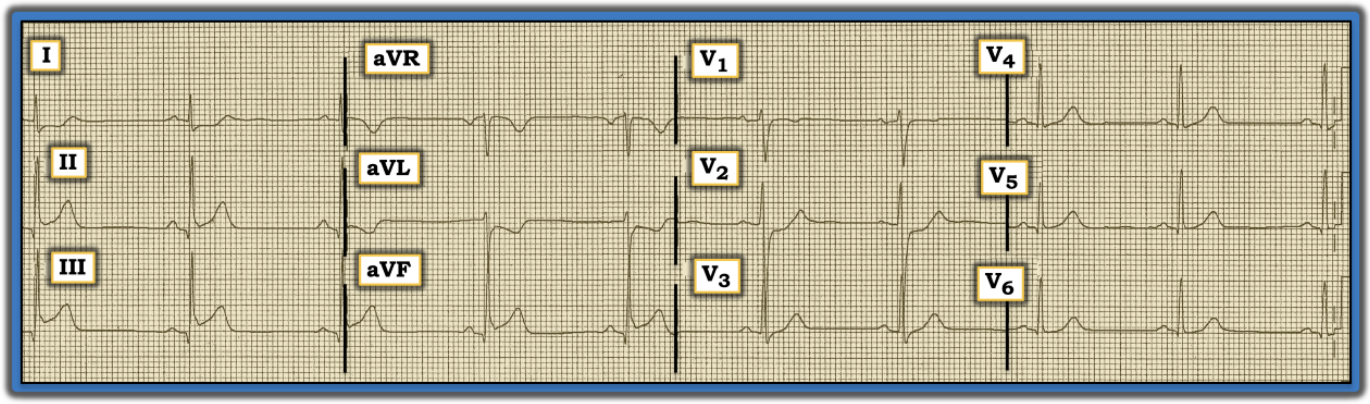
Dr. Grauer reports no financial relationships relevant to this field of study.

This ECG Was in Your 'Pile to be Read'

Imagine the ECG in the figure below was one of many tracings you received to read from a group of patients seen by other providers in your clinic. Unfortunately, no clinical information about this patient was available. How would one interpret this tracing? Considering no clinical information regarding what happened to the patient was available, what is the next step?



Clearly, this tracing is of concern. The rhythm is sinus bradycardia at a rate just under 60 beats/minute. All intervals (PR/QRS/QTc) are normal. The axis is normal at +75 degrees. There is no chamber enlargement. Small q waves are seen in the inferolateral leads.

Regarding R wave progression, transition occurs normally here (i.e., between leads V2 and V3), although R wave amplitude in lead V2 is taller than is usually seen in this anterior lead. However, the most concerning findings relate to ST-T wave changes. In addition to those narrow inferior lead q waves, there is 1-1.5 mm of upward concavity ST segment elevation in each inferior lead.

There are several reasons to suspect this represents an acute (or at least recent) inferior infarction. One, there is mirror-image opposite ST segment depression in lead aVL. Two, there is 1 mm of flat ST depression in lead I. Three, there also is ST depression in lead V2 in association with a taller-than-expected R wave in this anterior lead.

The ECG findings described so far strongly suggest recent (if not acute) inferoposterior myocardial infarction (MI). There is a "magic," mirror-image opposite relationship that is seen commonly in acute inferior MI between the appearance of the ST segment and T wave in lead III, compared to the ST-T wave in lead aVL. If one mentally "flips" the shape of the elevated ST-T wave seen in lead III, the result closely resembles the J-point depression and sagging ST segment seen in lead aVL. The finding of a taller-than-expected R wave in anterior lead V2, in association with the depressed ST segment in this anterior lead, strongly suggests recent posterior MI. Putting these findings together makes for no fewer than six leads (i.e., leads I, II, III; aVL, aVF; and V2) that suggest recent (if not acute) inferoposterior MI has occurred. Immediately search for the chart of the patient whose ECG is shown in the figure to find out whether the caring provider recognized these ECG changes. If not, find the patient.

NOTE: For more information about and further discussion on this case, please visit: http://bit.ly/3cLJZbq.