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ABSTRACT & COMMENTARY

Apolipoprotein E and CSF Levels in Men and Women With Alzheimer's Disease

By Lisa Mosconi, PhD

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

SYNOPSIS: Apolipoprotein E epsilon 4 (APOE4) genotype, the stronger genetic risk factor for late-onset Alzheimer's disease, negatively affects cerebrospinal levels of tau protein in a sex-dependent manner, whereby the effect of APOE4 is stronger in women than men.

SOURCE: Hohman TJ, Dumitrescu L, Barnes LL, et al. Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. *JAMA Neurol* 2018;75:989-998.

It long has been known that the prevalence of Alzheimer's disease (AD) is higher in women than in men, even accounting for women's increased longevity relative to men.[1] Further, the epsilon 4 variant of the apolipoprotein E gene (APOE4), the strongest genetic risk factor for late-onset AD, increases AD risk in a sex-dependent manner. The strength of the association varies by age, with female APOE4 carriers aged 55-70 years at highest risk.[2] To address the gender disparity in AD prevalence, efforts toward understanding sex-specific differences in disease etiology, manifestation, and progression have begun to emerge. Hohman et al conducted a multicohort study that combined data from 10 longitudinal cohort studies of normal aging and AD. The goal of the study was to examine sex-dependent effects of APOE genotype on markers of AD pathology in vivo and ex vivo.

The first set of analyses focused on four in vivo data sets that included cerebrospinal fluid (CSF) levels of beta-amyloid 42, total tau, and hyperphosphorylated tau measures collected from 1,798 patients, 48% of whom were women. The second set of analyses focused on six autopsy data sets leveraging direct measures of AD neuropathology, including Consortium to Establish a Registry for Alzheimer's Disease (CEDAR) staging for neuritic plaques and Braak staging for neurofibrillary tangles, obtained from 5,109

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patients, including 55% women. Of the 1,798 patients in the CSF biomarker cohort, 862 were women, 226 had AD, 1,690 were white, and the mean age was 70 years. Of the 5,109 patients in the autopsy cohort, 2,813 were women, 4,953 were white, and the mean age was 84 years. After correcting for multiple comparisons, the authors found a statistically significant interaction between APOE4 and sex on CSF total tau and phosphorylated tau ($P \leq 0.001$). APOE4 showed a stronger association among women than men. On post-hoc analysis, this sex difference was present in amyloid-positive individuals but not amyloid-negative individuals. No interactions between APOE4 and sex were found on postmortem measures.

■ COMMENTARY

These findings provide robust evidence of sex differences in the association between APOE4 and CSF tau levels. The authors found the effect of APOE was stronger in women than men. The observed sex difference was driven by amyloid-positive individuals, which suggests that APOE may confer sex-specific risk for downstream neurodegeneration in the presence of enhanced amyloidosis.

These results point to several sex-driven mechanisms that could underline this sex difference in tau, especially hormonal changes that occur during and after menopause, representing the strongest candidate pathway. For example, other researchers have found evidence that lower estrogen levels in women could lead to a more severe downstream response to amyloidosis,[3] an effect that could be enhanced among APOE4 carriers. Alternatively, late-life changes in estrogen levels in women directly affect tau. In fact, in female rats, estradiol appears to protect against tau hyperphosphorylation.[4]

These data are consistent with recent brain imaging studies showing that, among middle-aged women at risk for AD, those at the perimenopausal and postmenopausal stages exhibit emergence and progression of an AD endophenotype characterized by increasing beta-amyloid deposition, declines in glucose metabolism, and smaller brain volumes.[5-7] Amyloid deposition was more pronounced in APOE4 carriers than noncarriers.[5] No such abnormalities were observed in age-matched men, suggesting that AD-related pathological changes and their downstream effects on neuronal function affect women's brains earlier than men's brains.

[These results point to several sex-driven mechanisms that could underline this sex difference in tau, especially hormonal changes that occur during and after menopause, representing the strongest candidate pathway.]

More research is needed to evaluate the genetic drivers of plaques, tangles, neurodegeneration, and cognitive impairment in a sex-specific manner to identify novel pathways of risk. ■

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ABSTRACT & COMMENTARY

Clinical Outcomes After Oral Anticoagulant-Associated Intracerebral Hematoma

By Santosh Murthy, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In this meta-analysis of multiple observational studies, clinical outcomes after oral anticoagulant-associated intracerebral hematoma were similar for those associated with vitamin K antagonists or the new class of direct oral anticoagulants.

SOURCE: Tsivgoulis G, Wilson D, Katsanos AH, et al. Neuroimaging and clinical outcomes of oral anticoagulant-associated intracerebral hemorrhage. *Ann Neurol* 2018;84:694-704.

In about one-fifth of patients with primary intracerebral hemorrhage (ICH), the condition has been found to be related to anticoagulant use. Historically, vitamin K antagonists (VKAs), such as warfarin (once widely accepted as the oral medication of choice), were associated independently with higher admission hematoma volumes, hematoma expansion, higher mortality, and more severe disability compared to patients not on anticoagulant medications. The advent of nonvitamin K antagonists, direct oral anticoagulants (DOACs) has added a new dimension to the field of anticoagulation.

The authors of randomized, clinical trials in patients with atrial fibrillation have demonstrated conclusively that the risk of ICH is significantly lower with DOACs compared to VKAs, while the antithromboembolic benefit is similar. However, head-to-head comparisons of ICH outcomes in patients on these medications have yielded conflicting results, given limitations of low power, retrospective design, and mostly single-center data.

Tsivgoulis et al presented an individual patient data meta-analysis in which they compared 219 patients with DOAC-associated ICH with 831 with VKA-related ICHs across seven published, international, observational studies. The primary outcome was 30-day all-cause mortality, while thesecondary outcomes included clinical ICH severity, hematoma expansion, and functional outcomes at prespecified time points. The authors showed that DOAC use was associated with milder ICH clinical severity, as evidenced by lower National Institutes of Health Stroke Scale scores and smaller admission hematoma volumes, compared to VKA use. However, there were no differences in 30-day mortality (24.3% vs. 26.5%; hazard ratio, 0.94; 95% confidence interval [CI], 0.67-1.31), functional outcomes between the two groups at hospital discharge (common odds ratio, 0.78; 95% CI, 0.57-1.07), or functional status at three months (common OR, 1.03; 95% CI, 0.75-1.43) after adjusting for potential confounders, such as demographics and clinical and radiological characteristics of ICH.

■ COMMENTARY

This individual patient data meta-analysis highlights important baseline clinical and radiological characteristics of DOAC-ICH compared to VKA-ICH. These results are in stark contrast to those reported in a large retrospective cohort study using the American Heart Association's Get With the Guidelines registry of nearly 150,000 ICH patients, which revealed that DOAC-ICH led to lower inpatient mortality and favorable discharge disposition compared to VKA-ICH. However, the results were not adjusted for baseline clinical or radiological ICH severity, which likely confounded the multivariable analyses. One may surmise that selective inhibition of the extrinsic coagulation pathway and shorter half-life of DOACs confer a pharmacologic advantage over VKAs.

With emerging data tipping the balance in favor of DOACs as the oral anticoagulant medication of choice, studies with longer follow-ups of six months to one year are warranted, since the trajectory for recovery after ICH often is slower than that of ischemic stroke.

Current data suggest that rates of mortality and disability are relatively similar between VKA- and DOAC-associated ICH. Emerging data suggest that DOACs have smaller baseline hematoma volumes. As for the risk of ICH, DOACs appear to carry a significantly lower risk compared to VKAs. However, the antithromboembolic benefit is similar between the two groups. Although the prothrombin complex concentrates are used widely to reverse coagulopathy associated with warfarin use, specific medications, such as idarucizumab and andexanet, are now available as reversal agents for DOACs. ■

ABSTRACT & COMMENTARY

Combination Drug Therapy for Hypertension

By Michael H. Crawford, MD

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

SYNOPSIS: A large regional database study from Italy revealed that initial combination therapy for newly diagnosed hypertension results in fewer major adverse cardiovascular events at one year compared to monotherapy.

SOURCE: Rea F, Corrao G, Merlino L, Mancia G. Early cardiovascular protection by initial two-drug fixed-dose combination treatment vs. monotherapy in hypertension. *Eur Heart J* 2018;39:3654-3661.

Although many guidelines recommend initial treatment of hypertension with two drugs, especially if the systolic blood pressure (BP) is > 160 mmHg, there are little data on whether this approach improves cardiovascular (CV) outcomes.

Investigators from Milan performed an observational study comparing initial use of monotherapy vs. two-drug therapy to determine if CV outcomes were different at one year. A case-controlled model was used to minimize confounding. Subjects were identified in the Lombardy region National Health Service database, which includes more than 5 million individuals who received at least one new prescription for an antihypertensive medication and no antihypertensive drug prescriptions in the preceding 10 years. Patients were between the ages of 40 and 80 years and were compliant with therapy. Since most combination therapy in Italy used fixed-dose combinations, patients who received multiple individual prescriptions were excluded. Also, none of the combination pills integrated angiotensin modulators and calcium antagonists at the time the initial data were obtained. The primary endpoint was hospitalization for a CV event.

A total of 44,534 patients met inclusion criteria. Of these patients, 83% started therapy on one drug and 17% started therapy on two drugs. Seventy-seven percent of combination therapies were with an angiotensin modulator and a diuretic. The most common monotherapy was with an angiotensin modulator (68%). Adherence to therapy was similar in both groups (about 75%). After adjustment for covariates, there was a significant (21%) reduction in CV events at one year for the combination therapy patients compared to monotherapy (hazard ratio, 0.79; 95% confidence interval [CI], 0.71-0.88; $P < 0.01$). This difference also was observed for the individual endpoints of ischemic heart disease (-39%) and atrial fibrillation (-37%). In addition, the frequency of CV events in those on monotherapy was highest in the first month after starting therapy, decreasing incrementally until six months. The authors concluded that initial combination therapy is more effective at preventing CV events over one year than initial monotherapy.

■ COMMENTARY

Several rationales for using initial combination therapy for hypertension have been demonstrated. First, this approach lowers BP to target more rapidly, which may be important in patients at high risk for CV events. Second, adherence is better with combination therapy, possibly because of the positive feedback of the lower BP. Third, combination therapy has been associated with better BP control for up to one year, probably because it reduces the inertia of titrating monotherapy. Fourth, by using low doses of multiple drugs with different adverse effect profiles, synergistic BP lowering is accomplished without increasing side effects. However, limited data exist on whether initial combination therapy improves outcomes, which was the aim of this Italian study.

There were several strengths to this study. It was conducted in a general population, not selected trial participants. Participants experienced many CV events. The outcomes data were verified three ways: adjusted

for comorbidities, case-matched analysis, and a unique technique whereby patients were used as their own controls. The latter involved finding patients who took monotherapy for some period and combination therapy for a different period and experienced at least one CV event. This analysis showed a large CV event incidence ratio reduction (IRR) in favor of combination therapy (IRR, 0.44; 95% CI, 0.40-0.49).

The major weakness of the study was that the data do not tell us why these differences exist. Adherence rates were similar, but no BP data were available from the database used. Also, there were no laboratory data to identify potential drug toxicities. In addition, the newer combination pills with angiotensin modulators and calcium antagonists were not studied. Based on comparison studies, these newer combinations might have provided bigger differences in CV outcomes.

It is noteworthy that only about one in five patients in this study started combination therapy despite previous positive data and the recommendations of national guidelines. Perhaps this was because of the paucity of outcome data and slow acceptance of combination pills by insurers. Hopefully, this study will help eliminate this acceptance gap. In the United States, there are many generic combination pills, so this barrier has been eliminated. All that remains is convincing physicians and patients that the evidence favors initial combination therapy for hypertension. ■

BRIEF REPORT

Homeless Population Requires Hepatitis A Vaccination

By Carol A. Kemper, MD, FACP

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

SOURCE: Foster M, Ramachandran S, Myatt K, et al. Hepatitis A virus outbreaks associated with drug use and homelessness — California, Kentucky, Michigan, and Utah, 2017. *MMWR Morb Mortal Wkly Rep* 2018;67:1208-1210.

A multistate outbreak of hepatitis A virus (HAV) infection in the homeless and/or drug-using population has prompted the United States Advisory Committee on Immunization Practices to add "homelessness" as an indication for HAV vaccination, effective Oct. 24, 2018. This is in addition to existing indications for HAV vaccination of men who have sex with men (MSM) and illicit drug users (with the exception of marijuana use).

During 2017, 1,521 outbreak cases of acute HAV infection were reported in California, Kentucky, Michigan, and Utah, mostly in the homeless and/or drug-using population. An outbreak case was defined as acute HAV infection with a viral specimen matching the outbreak strain or if the case could be linked with another identified case. Although HAV generally is transmitted by close personal or sexual contact and unsanitary conditions, this was the first time an outbreak was fueled in part by parenteral transmission from contaminated needles and other shared paraphernalia. This shift in the epidemiology of HAV infection raised alarms for health officials.

Forty-one of outbreak cases died and 1,073 were hospitalized. Three percent had confirmed hepatitis B coinfection and 22% had confirmed or probable hepatitis C coinfection. Fifty-seven percent reported homelessness and/or drug use, and 5% were MSM.

Increasingly, molecular techniques are used to identify outbreaks of HAV infection. For this investigation, serum samples submitted to the CDC were used to extract and amplify a fragment of the VP1/P2B region of the virus for genetic characterization. A total of 1,054 specimens were tested, 96% of which were positive for genotype 1b virus, which generally is an uncommon strain. Most clinical cases of HAV infection in the United States before 2017 have been due to genotype 1a virus. The genotype 1b strain circulating in California, Utah, and Kentucky was different from that found in Michigan.

In California, the outbreak started in San Diego County in November 2016 and quickly spread to Los Angeles, Santa Cruz, and Monterey counties. In October 2017, Gov. Jerry Brown declared a state of emergency to secure many vaccine doses. Three California counties mounted an offensive, deploying vans to homeless encampments and distributing alerts to local clinics and emergency rooms. Approximately 123,000 doses of HAV vaccine were dispensed, effectively quelling the outbreak.

Although aggressive public health intervention in California stopped the outbreak there, it continues in Kentucky, Michigan, and Utah and may be spreading to other states. As of October 2018, more than 7,000 cases of acute HAV infection have been reported from 12 states. ■

PHARMACOLOGY UPDATE

Caplacizumab-yhdp for Injection (Cablivi)

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 the first therapy for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP). Caplacizumab-yhdp is a von Willebrand factor (vWF)-directed antibody fragment produced by recombinant DNA in *Escherichia coli* bacteria. The drug is considered a "nanobody," a novel class of therapeutic proteins that are fragments of antibodies. It is marketed as Cablivi.

INDICATIONS

Caplacizumab-yhdp is indicated for the treatment of aTTP in combination with plasma exchange and immunosuppressive therapy.[1]

DOSAGE

The recommended dose is 11 mg as an IV bolus at least 15 minutes prior to plasma exchange and 11 mg subcutaneously (SQ) after completion of plasma exchange on day 1.[1] Subsequent treatment is 11 mg SQ once daily following plasma exchange. This is followed by 11 mg SQ once daily for 30 days beyond the last plasma exchange. Depending on signs of persistent underlying disease (e.g., suppressed ADAMTS13 activity), treatment may be extended for a maximum of 28 days. If the patient experiences more than two recurrences of aTTP, caplacizumab-yhdp should be discontinued. Caplacizumab-yhdp is available as an 11 mg lyophilized powder in a single-dose vial.

POTENTIAL ADVANTAGES

Caplacizumab-yhdp plus plasma exchange is associated with faster normalization of platelet count and a lower incidence of aTTP-related death and recurrence.[1,2]

POTENTIAL DISADVANTAGES

Bleeding-rated adverse events (mainly mucocutaneous) were more common in patients taking caplacizumab-yhdp compared to those on plasma exchange plus placebo (65% vs. 48%).[1,2]

The rate of serious adverse events of bleeding was 11% for caplacizumab-yhdp vs. 1% for placebo.

COMMENTS

aTTP is caused by the development of autoantibodies that inhibit the activity of the vWF-cleaving protease ADAMTS13.[3] The result is hemolytic anemia, thrombocytopenia, and tissue infarction. Caplacizumab-yhdp binds to vWF, inhibiting the binding between vWF and platelets and reducing vWF-mediated platelet adhesion and consumption.[1]

The efficacy of caplacizumab-yhdp was evaluated in a randomized, double-blind, placebo-controlled study that included 145 subjects with aTTP.[1,2] Subjects were randomized to caplacizumab-yhdp or placebo in addition to standard care, which was defined as daily plasma exchange up to two days after normalization of platelet count (≥ 150,000 µL). Prednisone or prednisolone was administered during the plasma-exchange period and continued for the first week, after which it could be tapered and discontinued within 30 days after the last plasma exchange. Caplacizumab-yhdp was continued for 30 days after completion of plasma exchange and could be extended at seven-day intervals up to 28 days. The primary endpoint was the time to normalization of platelet count. Secondary endpoints were a composite of aTTP-related death, recurrence of aTTP, or a major thromboembolic event.

The median time to platelet response was statistically shorter with caplacizumab-yhdp (2.69 vs. 2.88 days; $P = 0.01$). There were nine events in the caplacizumab-yhdp group compared to 36 events for placebo ($P < 0.0001$). There were zero deaths, three patients with recurrence of aTTP, and six patients with major thromboembolic events in the caplacizumab-yhdp group. The corresponding events in the placebo group were three deaths, 28 patients with recurrence of aTTP, and six patients with major thromboembolic events. The caplacizumab-yhdp group demonstrated a lower volume of plasma exchange (median 18.1 L vs. 26.9 L in the placebo group), fewer days of hospitalization (median nine days vs. 12 days in the placebo group), and fewer days in the ICU (median three days vs. five days in the placebo group).[2]

CLINICAL IMPLICATIONS

aTTP is a rare and life-threatening disorder.[4] Current treatment calls for plasma exchange to replenish functioning ADAMTS13 and remove vWF autoantibodies. Glucocorticoids are administered to suppress anti-ADAMTS13 autoantibodies.[2] The addition of caplacizumab-yhdp accelerates platelet recovery, lowers adverse outcomes (composite of death and recurrence), and possibly reduces healthcare resource use.

The estimated average cost for treating a typical aTTP episode with caplacizumab-yhdp is $270,000. ■

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CME QUESTIONS

1. **A 69-year-old male diagnosed with new-onset paroxysmal atrial fibrillation presents for a second opinion regarding choice of anticoagulation between direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs). Which of the following statements is true?**
   a. DOACs and VKAs carry a similar risk of intracerebral hemorrhage (ICH).
   b. DOACs are inferior to VKAs in preventing incident thromboembolic events.
   c. ICH associated with DOAC use leads to similar mortality and disability rates compared to ICH resulting from VKA use.
   d. Specific medications to reverse coagulopathy are available for VKAs but not DOACs.

2. **Initial combination drug therapy vs. monotherapy resulted in which of the following at one year?**
   a. Fewer cardiovascular events
   b. Worse adherence to drug therapy
   c. More admissions for hypotension
   d. More acute kidney injury

3. **Which of the following was first added in the past year as an indication for vaccination against hepatitis A virus infection?**
   a. Homelessness
   b. Traveling to developing countries with high or intermediate hepatitis A endemicity
   c. Significant exposure to hepatitis A
   d. Chronic hepatitis B or C infection

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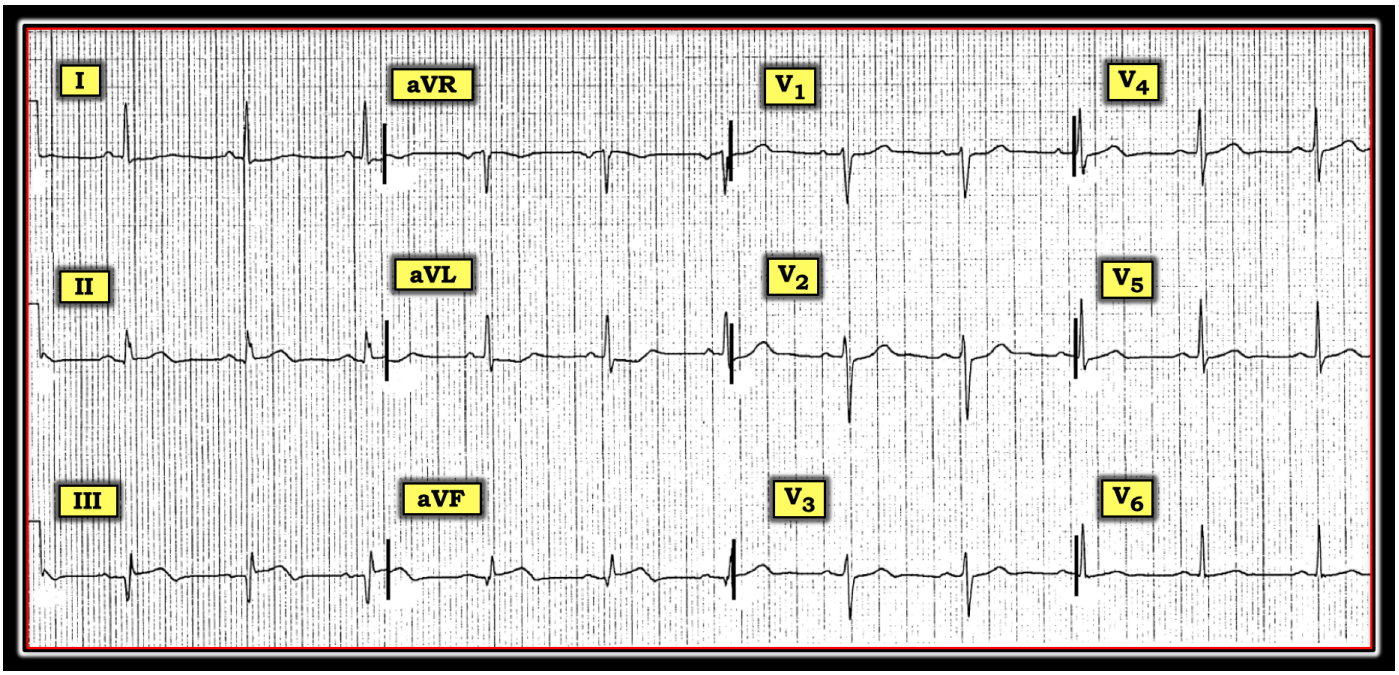
Dr. Grauer reports no financial relationships relevant to this field of study.

Are the Changes Acute?

Imagine the ECG in the figure below was obtained from a previously healthy, middle-aged man who presented to an ambulatory clinic for "indigestion." How might one interpret this ECG? Are there acute changes?



The rhythm is sinus at a rate of ~70 beats/minute. All intervals and the mean QRS axis are normal. There is no chamber enlargement. A large Q wave is seen in lead III and small Q waves are present in leads II and aVF. Transition is normal (occurs between V3 to V4). There is coved ST elevation in leads III and aVF, with a hint of early T-wave inversion in these leads. There also appears to be slight-but-real ST elevation in lead II. ST depression is seen in lead I (slightly), in lead aVL (more definite), and probably also in lead V2. The T wave is relatively flat in leads V5 and V6 (normally, the T wave is clearly upright in these lateral chest leads). The combination of these findings suggests we should assume inferior myocardial infarction (MI) has occurred at some point, probably in the recent past (at least until proven otherwise). The challenge is to determine the relative age of this MI, since treatment recommendations will vary dramatically depending on the answer.

ECG findings suggesting a more acute MI: There is ST elevation in each of the inferior leads; there is reciprocal ST depression in lead aVL, best appreciated by the fact that ST-T wave appearance in lead aVL is the *mirror image* picture of the ST-T wave in lead III.

ECG findings suggesting a less acute picture: The amount of ST elevation is relatively modest, a huge Q wave has formed already in lead III, the amount of reciprocal ST depression is extremely modest, and the patient presented to an ambulatory clinic instead an ED. Further, there is no specific history for acute-onset chest pain. Although patients with acute MI certainly can present to an ambulatory clinic, there seems to be a "self-selection" process, whereby statistical likelihood of an acute event appears to be greatly enhanced when patients call 911 and present with their symptoms to the ED instead of to an outpatient clinic. Pending additional historical information, the overall picture suggests a less acute onset for this MI. Whether this dates this infarct to 12 to 24 hours ago (or even longer ago than that) is uncertain from the information available.

For more information about and further discussion on this case, please visit: https://bit.ly/2S31iZW.