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ABSTRACT & COMMENTARY

Thin Evidence Supporting the Obesity Paradox in STEMI

By Jeffrey Zimmet, MD, PhD

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

SYNOPSIS: This largest-to-date analysis of six randomized studies of ST-elevation myocardial infarction revealed no association between body mass index and infarct size, one-year mortality, or heart failure hospitalization.

SOURCE: Shahim B, Redfors B, Chen S, et al. BMI, infarct size, and clinical outcomes following primary PCI: Patient-level analysis from 6 randomized trials. *JACC Cardiovasc Interv* 2020;13:965-972.

The "obesity paradox" refers to the observation that although obesity contributes to many risk factors that make cardiovascular disease more likely, obese people may fare better than their normal weight counterparts in acute exacerbations of disease, such as acute myocardial infarction (MI). In ST-elevation MI (STEMI) in particular, the evidence in this area has been mixed. Yet a host of data have been built up supporting the putative obesity advantage. Some, but not all, prior studies have revealed smaller infarct sizes among overweight patients. Experimental models have demonstrated the ability of hormones produced by adipose tissue to reduce infarct size in mice. To examine this question, Shahim et al combined patient-level data from six contemporary randomized trials of patients receiving primary percutaneous coronary intervention (PCI) for STEMI. The authors of each trial measured infarct size at a median of four days after an event, with five using cardiovascular magnetic resonance (MR) and one using 99mTc-sestamibi SPECT/CT. All collected data on body mass index (BMI), and each reported clinical endpoints that were adjudicated by independent clinical events committees.

Among the six trials, data were available for 2,238 patients with STEMI undergoing primary PCI. Analyses were performed using BMI as a continuous variable and with patients stratified according to the World Health Organization (WHO) definitions of normal weight, overweight, and obese. Among the patients

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analyzed for the study, 658 were classified as normal weight, 1,008 were overweight, and 586 were obese. Regarding baseline characteristics, overweight and obese patients were more likely than normal weight patients to have diabetes, hypertension, and hyperlipidemia, but were less likely to smoke. No significant differences were seen among the BMI groups when it came to presentation of the acute MI itself.

Regardless of whether BMI was treated as a continuous variable or a categorical one, Shahim et al found no association between BMI and infarct size, microvascular obstruction, or ejection fraction (EF). During a median follow-up of 350 days, there was no unadjusted or adjusted association between BMI and the rates of death or heart failure hospitalization. Similarly, when stratified by WHO classification, these outcomes were similar among normal, overweight, and obese individuals. The authors concluded that among patients undergoing primary PCI for STEMI, there was no protective effect of increased BMI on infarct size, microvascular obstruction, EF, or one-year rates of death and heart failure hospitalization.

■ COMMENTARY

In several ways, this study was specific, dealing only with STEMI patients undergoing primary PCI and weighted toward anterior infarct and larger infarcts. Unfortunately, there was no insight regarding procedural complications, which elsewhere have been observed less often in overweight patients. By design, patients with poor early outcomes who did not make it to imaging evaluation were excluded from the analysis.

The authors acknowledged BMI is a highly imperfect measure of obesity, and that other measures, such as waist circumference and fat mass index, may be relatively advantageous. Regardless, this was by far the largest study to date of the relationships between obesity (as measured by BMI) and infarct size and hard clinical outcomes after STEMI. Most of the 2,238 subjects were evaluated by cardiac MR, which likely is the best modality for this evaluation. Three prior reports that used cardiac MR for infarct size included 89, 193, and 426 patients. Overall, Shahim et al conducted an excellent study. Their work represents the best effort to date to provide a definitive conclusion on this issue. For now, the best available evidence suggests overweight and obese patients have no advantage in terms of outcomes in STEMI — but no detriment, either. In this regard, the obesity paradox remains a point for discussion. ■

ABSTRACT & COMMENTARY

Inappropriately Broad Empiric Antibiotics, Higher Mortality, and Community-Onset Sepsis

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 retrospective cohort study revealed broad-spectrum antibiotics were unnecessarily prescribed to patients with community-onset sepsis and were associated with worse outcomes and higher mortality.

SOURCE: Rhee C, Kadri SS, Dekker JP, et al. Prevalence of antibiotic-resistant pathogens in culture-proven sepsis and outcomes associated with inadequate and broad-spectrum empiric antibiotic use. *JAMA Netw Open* 2020;3:e202899.

In the management of sepsis, early administration of empiric antibiotic therapy is a critical step. However, overtreatment (i.e., unnecessary broad-spectrum therapy) can produce adverse reactions, lead to potential selection for antibiotic-resistant bacteria, *Clostridioides difficile* infection (CDI), and cost more. Inappropriately narrow therapy

can lead to higher mortality. Rhee et al examined the outcomes associated with overtreatment and undertreatment in patients with culture-positive community-onset sepsis.

The authors conducted a retrospective cohort analysis using data from a diverse group of U.S. hospitals. Included patients were ≥ age 20 years, had received a diagnosis of community-acquired sepsis, and had positive cultures for potentially pathogenic organisms by hospital day 2. Patients were excluded if they had hospital-acquired sepsis or were transferred from long-term care or rehabilitation facilities, hospice, or other hospitals. The authors used ICD-9-CM discharge codes to diagnosis sepsis. The investigators considered patients to have received inadequate empiric therapy if at least one pathogen isolated from any clinical culture was not susceptible to all antibiotics administered during the initial two days of admission. They considered patients to have received unnecessarily broad empiric therapy if they were prescribed anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics, anti-vancomycin-resistant enterococci (VRE) antibiotics, anti-*Pseudomonas* β-lactams or carbapenems but none of the organisms targeted by these antibiotics were recovered. The primary outcome was in-hospital mortality.

The cohort included 17,430 patients. The median age was 69 years, and 55.9% were women. Urinary tract infection was the most common source of sepsis (48.9%), followed by pulmonary (32.9%), intra-abdominal (13.6%), and skin and soft tissue (10.3%) infections. The most frequently identified pathogens were *Escherichia coli* (33.7%), *Staphylococcus aureus* (21.3%), *Streptococcus* spp. (13.5%), *Klebsiella* spp. (12.9%), and *Enterococcus* spp. (11.1%). Antibiotic-resistant organisms included MRSA (11.7%) and ceftriaxone-resistant gram-negative organisms (CTX-RO) (13.1%). Of these, 66.3% had *P. aeruginosa*, VRE (2.1%), extended spectrum beta-lactamases (ESBLs) (0.8%), and carbapenem-resistant *Enterobacteriaceae* (CRE) (0.5%). The prevalence of at least one resistant gram-positive organism (MRSA or VRE) was 13.6%, while 13.2% of the cohort had at least one resistant gram-negative organism. Patients with resistant organisms were more likely to have a great number of comorbidities, have a pulmonary infection, require vasopressors or mechanical ventilation, be admitted to the intensive care unit, and die in the hospital.

The most commonly prescribed antibiotic was vancomycin, received by 41.7% of patients, followed by a fluoroquinolone (40.1%), piperacillin-tazobactam (33.9%), and ceftriaxone (29.8%). Overall, 11,797 patients received antibiotic therapy directed against the antimicrobial-resistant (AMR) pathogens listed earlier. Of these patients, 3,447 had at least one of these organisms isolated in culture. The empiric antibiotics were active in 12,398 out of 15,183 cases of sepsis in which antibiotic-pathogen susceptibility combinations could be examined. A multivariable analysis determined inadequate therapy was significantly associated with higher mortality (adjusted odds ratio [aOR], 1.19; 95% confidence interval [CI], 1.03-1.37; $P = 0.02$). This held true after adjusting for baseline characteristics, severity of illness, and adequacy of therapy. Unnecessarily broad antibiotic therapy was associated with higher mortality in patients without shock (aOR, 1.22; 95% CI, 1.06-1.49; $P = 0.007$), as well as a greater risk for CDI (aOR, 1.26; 95% CI, 1.01-1.57; $P = 0.04$). There also was a trend toward more acute kidney injury that did not reach statistical significance. Vital sign data during the first two days of hospitalization were reported missing in 47.8% of cases, while lactic acid levels (an important marker for sepsis and septic shock) were missing in 40.9%.

■ COMMENTARY

Clinicians are well aware of the mantra to recognize and treat sepsis early. But pragmatically, it is challenging to estimate accurately which patients might have an infection because of an AMR organism. Although risk factors (e.g., prior AMR infection, recent antibiotic use, recent hospitalization, and underlying comorbidities) may be helpful, they are not foolproof. Thus, a trade-off exists between choosing empiric antibiotics with a spectrum that is too broad vs. one that is too narrow. Rhee et al provided some useful information for dealing with this common clinical scenario, yet highlights limitations in the diagnostic process. Most patients with community-onset sepsis do not have AMR pathogens, so treating them with broad-spectrum antibiotics is inappropriate. That said, identifying the small fraction who do is limited by the widespread lack of rapid diagnostic testing. Better prediction models to determine the risk of an AMR infection that is assessed in many patients with sepsis also could help inform empiric antibiotic decisions.

A major limitation of the study is that in approximately 30% to 50% of sepsis cases, cultures were negative or the exact source of sepsis was not clearly determined. The reliance on culture data in this study almost certainly led to an overestimate of resistant pathogens in the cohort. Another limitation is related to the observation that more severely ill patients received broad-spectrum antibiotics, which, in fact, may have been because of residual confounding in this group related to the wide range of organ dysfunction. Finally, limitations in the data set mean the investigators did not have information on patient allergies, potential complications of antibiotics, or whether patients were hospitalized recently.

Most patients with community-acquired sepsis do not have resistant organisms, but inadequate therapy in those who do leads to higher mortality. This is another reminder that we need faster and more accurate diagnostic tests to optimize the management of patients with sepsis. ■

ABSTRACT & COMMENTARY

COVID-19 and Steroids: Is There a Consensus?

By Kathryn Radigan, MD, MSCI

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

SYNOPSIS: A study of adults admitted with COVID-19 pneumonia revealed risk factors associated with developing acute respiratory distress syndrome (ARDS) and progression from ARDS to death included older age, neutrophilia, organ dysfunction, and coagulation derangement.

SOURCE: Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:1-11.

Researchers continue scrutinizing risk factors for COVID-19. Wu et al performed a retrospective cohort study among 201 adults admitted to Jinyintan Hospital between Dec. 25, 2019, and Jan. 26, 2020, to describe the clinical characteristics and outcomes of COVID-19 patients with pneumonia. Of the 201 patients, 84 developed acute respiratory distress syndrome (ARDS), and approximately half of those died. When compared to non-ARDS patients, ARDS patients complained more often of dyspnea (59.5% vs. 25.6% patients; difference, 33.9%; 95% confidence interval [CI], 19.7%-48.1%). ARDS patients also had more comorbidities, including hypertension and diabetes.

Through a bivariate Cox regression analysis, researchers showed risk factors associated with ARDS and progression from ARDS to death, which included: older age (hazard ratio [HR], 3.26; 95% CI, 2.08-5.11; HR, 6.17; 95% CI, 3.26-11.67, respectively), neutrophilia (HR, 1.14; 95% CI, 1.09-1.19; HR, 1.08; 95% CI, 1.01-1.17, respectively), and organ and coagulation dysfunction based on higher lactate dehydrogenase (HR, 1.61; 95% CI, 1.44-1.79; HR, 1.30; 95% CI, 1.11-1.52, respectively) and D-dimer (HR, 1.03; 95% CI, 1.01-1.04; HR, 1.02; 95% CI, 1.01-1.04, respectively). Although high fever (≥ 39°C) was associated with higher likelihood of ARDS (HR, 1.77; 95% CI, 1.11-2.84), it also was associated with a lower likelihood of death (HR, 0.41; 95% CI, 0.21-0.82). ARDS patients treated with methylprednisolone were at a lower risk of death (HR, 0.38; 95% CI, 0.20-0.72).

Researchers concluded older age, hypertension, and diabetes are associated with worse outcomes. Although high fever was associated with ARDS development, it also was associated with better outcomes among patients with ARDS. In addition, treatment with methylprednisolone may be beneficial for patients who develop ARDS.

■ COMMENTARY

Learning more about how to treat COVID-19 optimally is not only profoundly important but has reached a state of emergency. COVID-19-related mortality in the United States is progressing rapidly to more than 147,000 patients, and proven treatments are bleak.[1] Shortly after there was evidence that cytokine storm syndrome was associated with the severity of ARDS in COVID-19,[2] corticosteroids became a treatment of great interest, mainly because of their profound anti-inflammatory and immunoregulatory properties. This study is one of the first that references the use of steroids in COVID-19 and boasts giving methylprednisolone to patients with ARDS may lower death risk.

Of course, these findings and statements must be interpreted cautiously based on this study. The authors openly discussed their concerns that the small sample size and observational nature of the study subject it to potential bias and residual confounding. Furthermore, there also is concern that patients who died in this study population were less likely to be treated with antiviral therapy, and the authors did not separate which patients received steroids and/or antivirals. There also was no information on the timing, dosage, or duration of steroids, and whether there were any corticosteroid-related complications observed in the patients who received them.

Although this study is fraught with concerns, the results of the RECOVERY trial are promising.[3] This study, conducted in the United Kingdom, was a randomized controlled trial that included 2,104 COVID-19 patients given dexamethasone 6 mg once daily by mouth or intravenously for 10 days. When compared to 4,321 patients who received standard care, dexamethasone reduced the death rate in mechanically ventilated patients by 35% and in oxygen-dependent patients by 20% without a benefit in patients who were not receiving respiratory support. In contrast to the

RECOVERY trial, the only other studies available are extremely limited. Another retrospective cohort study by Wang et al, limited to 46 patients, showed that low-dose and short-term methylprednisolone was associated with a shorter time to defervescence along with a more rapid improvement in oxygenation and radiographic abnormalities.[4] Patients on methylprednisolone were weaned off oxygen at a median of eight days vs. 14 days ($P < 0.001$) in the standard care group. Zhou et al validated the potential benefits of low-dose corticosteroids in a subset of critically ill patients with COVID-19 pneumonia. Interpretation of these data is extremely limited since there were only 15 patients and no control group.[5]

Expert opinion may be used to guide clinicians further but have not been updated since news of the RECOVERY trial. Currently, both the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend glucocorticoids should not be administered routinely to patients with COVID-19, except in the setting of an evidence-based indication, such as asthma or chronic obstructive pulmonary disease exacerbation, refractory septic shock, and adrenal insufficiency.[6,7]

In addition to the recommendations by the CDC and WHO, the Society of Critical Care Medicine (SCCM) provides a conditional, weak recommendation in favor of glucocorticoids for the sickest COVID-19 patients who are intubated with severe ARDS (PaO_2/FiO_2 ratio < 100).[8] If clinicians choose to administer glucocorticoids, the SCCM suggests they should begin within the first 14 days, doses should be low, and courses should be short. The Surviving Sepsis Campaign aligns with the SCCM, while the infectious disease guidelines recommend steroids should be restricted to randomized controlled trials.[9]

The initial rationale for not administering glucocorticoids routinely in the COVID-19 ARDS population is that there is evidence of potential harm for patients with other viral pneumonias (i.e., Middle East respiratory syndrome, influenza, and severe acute respiratory syndrome). The data supporting any benefit did not include a sufficient proportion of patients with viral pneumonia to inform safety.[10-12] In contrast, Fang et al demonstrated low-dose corticosteroid therapy did not delay viral clearance in COVID-19 patients.[13] Keeping the administered dose low also may alleviate concerns about secondary bacterial or fungal infections. It will be interesting to observe how these recommendations will be updated after these groups reconvene, and the RECOVERY trial is discussed further.[3] ■

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PHARMACOLOGY UPDATE

Fostemsavir Extended-Release Tablets (Rukobia)

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

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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 first-in-class human immunodeficiency virus-1 (HIV-1) attachment inhibitor. This drug should be used to treat HIV-1 infections in patients with multidrug-resistant HIV-1 who have failed their current antiretroviral regimen. Fostemsavir is a prodrug. Temsavir attaches to glycoprotein 120 (gp120) on the outer surface of HIV-1, interfering with binding to CD4 receptors, thereby blocking entry and infection of immune cells.[1,2] Fostemsavir received fast track, priority review, and breakthrough therapy designations. It is marketed as Rukobia.

INDICATIONS

Fostemsavir is indicated, with other antiretrovirals, to treat HIV-1 infections in heavily treatment-experienced adults with multidrug-resistant HIV-1 infections who are failing current regimens.[1] Failure may be because of resistance, safety, or intolerance.

DOSAGE

The recommended dose is one tablet taken orally twice daily without regard to food.[1] Fostemsavir is available as extended-release tablets, each containing 600 mg of fostemsavir (725 mg of fostemsavir tromethamine).

POTENTIAL ADVANTAGES

Fostemsavir provides a new mechanism of action against HIV-1 and is effective in significantly reducing HIV-1 viral load in treatment-experienced patients with multidrug-resistant HIV-1 infections.[1,3] It is the first orally administered agent approved for this indication. Both enfuvirtide and ibalizumab, with similar indications, require administration by injection. In vitro data indicate there is no cross-resistance between fostemsavir and other HIV-1 entry inhibitors (e.g., enfuvirtide, ibalizumab).[2]

POTENTIAL DISADVANTAGES

Fostemsavir may increase QTc intervals in susceptible patients, such as those with a history of QTc prolongation or those taking a drug with a known risk of causing arrhythmias (e.g., Torsade de Pointes).[1] Temsavir is a substrate of CYP3A isoenzyme; coadministration with a strong CYP3A inducer is contraindicated.[1] As with other antiretroviral therapies (ART), initial treatment may cause immune reconstitution syndrome. Patients with hepatitis B and/or C coinfection may experience elevation of hepatic transaminases.[1]

COMMENTS

The efficacy of fostemsavir was evaluated in a partly randomized, double-blind, placebo-controlled, 96-week trial.[1,3,4] Subjects were enrolled in a randomized or nonrandomized cohort. In the randomized cohort, subjects were required to have at least one, but no more than two, fully active and available antiretroviral agent(s) at screening. Subjects were randomized to fostemsavir (n = 203) or placebo (n = 69) in addition to their failing regimen (i.e., functional monotherapy) for eight days. After day 8, subjects received open-label fostemsavir and with investigators-selected optimized background therapy (OBT). In the nonrandomized cohort (n = 99), subjects had no fully active ART available at screening. All subjects took open-label fostemsavir plus OBT. The overall study population was male (78%), white (70%), median age 49 years, median baseline HIV-1 RNA was 4.6 $\log_{10}$ copies/mL, 86% had history of AIDS, 71% were treated for > 15 years, and 85% had exposure to ≥ 5 different HIV treatment regimens. The primary endpoint was mean decline in HIV-1 RNA from day 1 to day 8 compared to placebo.

At day 8 in the randomized cohort, fostemsavir achieved a mean decrease of 0.79 $\log_{10}$ copies/mL compared to a reduction of 0.17 $\log_{10}$ copies/mL for the placebo group, with 46% achieving > 1 $\log_{10}$ copies/mL decrease vs. 10% for the placebo group. Subjects with baseline viral load of > 1,000 copies/mL showed a reduction of 0.86 $\log_{10}$ (vs. -20 $\log_{10}$ for the placebo group). For those with baseline ≤ 1,000 copies/mL, the reduction was 0.22 $\log_{10}$ (+0.10 $\log_{10}$ for placebo).

At week 96, 60% of the subjects had HIV-1 RNA < 40 copies/mL. In the nonrandomized cohort, 37% had HIV-1 RNA < 40 copies/mL. Median increase in CD4+ was 205 cells/mm^3 (baseline 99 cells/mm^3) in the randomized cohort and +119 cells/mm^3 (baseline 41 cells/mm^3) for the nonrandomized cohort. The proportion of subjects who discontinued treatment because of adverse events at week 96 was 5% in the randomized cohort and 12% in the nonrandomized cohort.[1]

CLINICAL IMPLICATIONS

Fostemsavir represents the eighth class of HIV-1 antiviral agents and the third agent approved for salvage therapy. While all three are HIV-1 entry inhibitors, each has a different molecular target. Enfuvirtide is a gp41 fusion inhibitor and ibalizumab is a CD4 direct post-attachment inhibitor. Fostemsavir offers the first orally effective agent in this group. In patients with first regimen virologic failure, the new regimen options are based on the type of failing regimen.[5]

With second regimen failure, the new regimen is based on past and current genotypic ± phenotypic resistance testing and ART history using at least two (preferably three) fully active agents.[5] In heavily treated patients with multidrug-resistant HIV-1 infections with unsuppressed virus and limited options, treatment options include enfuvirtide, ibalizumab, and now fostemsavir. The latter offers a new mechanism of action and the convenience of oral dosing vs. twice-daily or every-two-weeks injections for enfuvirtide and ibalizumab, respectively. Fostemsavir also appears to lack cross-resistance to the other two entry inhibitors.[2] The cost for fostemsavir is $7,650 for a 30-day supply. ■

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CME QUESTIONS

1. **The obesity paradox in ST-elevation myocardial infarction patients refers to:**
   a. more capillary flow to the infarcted area.
   b. a lower incidence of myocardial infarction.
   c. more atherogenic comorbidities.
   d. reduced infarct size.

2. **In the study by Wu et al, the results suggested using methylprednisolone may be beneficial for COVID-19 patients with what concurrent condition?**
   a. Acute respiratory distress syndrome
   b. Hypercoagulable state
   c. Acute renal failure
   d. Multiorgan failure

3. **The RECOVERY trial revealed dexamethasone reduced the death rate by 35% in what population of COVID-19 patients?**
   a. Mechanically ventilated patients
   b. Hypercoagulable patients
   c. Diabetic patients
   d. Patients in multiorgan failure

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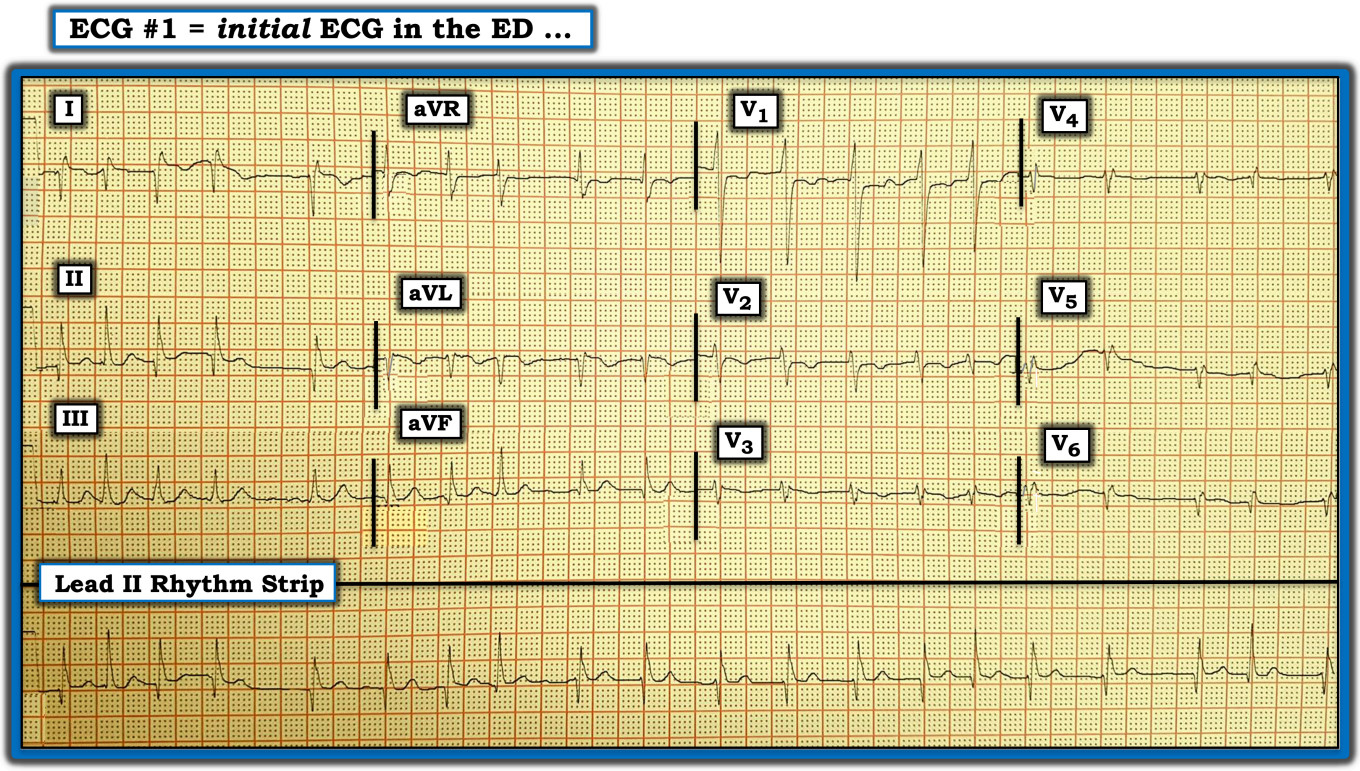
Dr. Grauer reports no financial relationships relevant to this field of study.

High Lateral Infarction, or Something Else?

The ECG in the figure below was obtained from a man with new onset palpitations. What is the probable cause of his symptoms? Is there high lateral infarction, or is something else accounting for the Q waves in leads I and aVL?



The long lead II rhythm strip at the bottom of the tracing shows the rhythm to be rapid, irregularly irregular, and without P waves. The rhythm is rapid atrial fibrillation. But there is much more. How often does one see Q waves this deep in lead I? Is R wave progression in the precordial leads normal?

It is extremely uncommon to see a QRS complex with a predominant Q wave in lead I, especially when the T wave in this lead also is negative (as seen in the figure). In combination with a significantly positive QRS complex in lead aVR, the predominant Q wave that visible in lead I should suggest the possibility of either lead reversal (caused by mix up of the left and right arm electrodes) or dextrocardia.

Dextrocardia is rare. Most providers can count on the fingers of one hand the number of cases they have seen during their careers. That said, there is reverse R wave progression in the chest leads of this tracing. That is, instead of the R wave progressively increasing in amplitude as one moves across the chest leads, the reverse occurs. The tallest R wave is in lead V1, after which R wave amplitude decreases. In fact, we see no more than highly unusual, low-amplitude rSr' complexes in leads V3 through V6 of this tracing.

This patient had dextrocardia. Heart sounds were heard on the right side of the chest, and a chest X-ray confirmed mirror-image reversal of the aortic knob and heart shadow. Follow-up ECG with chest leads placed on the right side of the chest showed a much more normal pattern of R wave progression.

For more information about and further discussion on this case, please visit: https://bit.ly/31VFbNY.