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Internal Medicine [ALERT]

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ABSTRACT & COMMENTARY

Heart Failure-Exacerbating Medications

By Michael H. Crawford, MD

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

SYNOPSIS: In a large, diverse cohort of Medicare patients hospitalized for heart failure exacerbations, almost half were on medications known to exacerbate heart failure; more than one-third were on these agents at discharge.

SOURCE: Goyal P, Kneifati-Hayek J, Archambault A, et al. Prescribing patterns of heart failure exacerbating medications following a heart failure hospitalization. *JACC Heart Fail* 2020;8:25-34.

Hospital admissions and readmissions due to heart failure (HF) exacerbations are common. Considerable national efforts have been invested in preventing them. However, little attention has been paid to concomitant therapy known to exacerbate HF.

The authors of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study identified Medicare beneficiaries > age 65 years with an adjudicated HF hospitalization between 2003 and 2014. In this diverse cohort, only hospitalizations > 90 days after eligible hospitalizations were included since earlier hospitalizations were likely to feature few medication changes. The HF-exacerbating medications were taken from the 2016 American Heart Association (AHA) Scientific Statement list of directly toxic medications and those that can exacerbate underlying myocardial dysfunction.[1] Only those medications classified as major exacerbating agents due to the potential for their life-threatening effects were studied.

A total of 558 unique patients with 723 unique hospitalizations were included. Their median age was 76 years; 44% were women, and 34% were black. The prevalence of HF-exacerbating medications was 41% at hospital admission and 36% at discharge. These patients were more likely to exhibit several comorbid conditions. The most frequently prescribed medications were albuterol, metformin, nonsteroidal anti-inflammatory drugs (NSAIDs), and diltiazem. During hospitalization, 17% reduced intake of their HF-exacerbating drugs, 19% took the same amount, 12% took more, and 51% were not taking any of these medications at admission or discharge. A multivariate analysis showed the factors most associated with potentially harmful

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prescribing were diabetes (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.18-2.75) and small hospital size (OR, 1.93; 95% CI, 1.18-3.16). The authors concluded that HF-exacerbating medications are initiated frequently or continued in Medicare patients admitted for HF.

■ COMMENTARY

The emphasis in HF management programs has been on guideline-based optimal medical therapy, not on avoiding drugs that could exacerbate HF. Thus, it is perhaps not surprising that almost half of older patients admitted for HF are on such medications. What is perhaps surprising is that potentially harmful drugs often are continued or even added during hospitalizations, such that 36% are discharged on these drugs. When I teach trainees about why patients experience HF exacerbation, I usually mention the five most common reasons: ischemia, arrhythmias, dietary indiscretion, medication noncompliance, and stress (e.g., infection). Now, we should add potentially harmful medications.

The AHA document lists dozens of agents with evidence for a casual role in HF exacerbations. Goyal et al focused on 22 such agents with the highest risk for harm. However, the level of evidence was not the same for each. For example, trastuzumab (Herceptin), a chemotherapy agent, carries level A evidence, NSAIDs level B, and metformin level C. Diabetes was one of the most common comorbidities leading to the prescription of potentially harmful drugs. Fortunately, there are newer drugs for diabetes that may help prevent HF (e.g., sodium-glucose transporter inhibitors). Obstructive airway disease was another common comorbidity, occurring in 30% of the Goyal et al cohort. Most drugs used for these pulmonary conditions can exacerbate HF (e.g., steroids, albuterol, antibiotics). These considerations point out one downside of disease-specific guidelines: therapeutic competition. The strengths of this study were that the results are generalizable due to the diversity of the patients and the 380 hospitals studied. Weaknesses included the consideration of only standing medication orders, which may have underestimated the number of patients receiving bronchodilators and NSAIDs. Some drugs, such as citalopram, are only toxic at extremely high doses or with significant renal dysfunction; their significance may be overestimated.

Clearly, this study shows that medication list management in hospitalized HF patients is suboptimal. This may be an area where the electronic medical record could help by flagging potentially harmful drugs if HF is on the admitting diagnoses list. All we need is another warning signal on the computer, so maybe there is a better way. There are pharmacists on our inpatient teams, and I am going to see if they can help me with this. ■

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ABSTRACT & COMMENTARY

Optimal Antithrombic Therapy After PCI for Atrial Fibrillation Patients

By Michael H. Crawford, MD

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

SYNOPSIS: In three subgroups of coronary artery disease patients with atrial fibrillation, apixaban plus a $P2Y_{12}$ inhibitor provided superior safety and similar efficacy outcomes as treatment with warfarin, aspirin, or both for six months.

SOURCE: Windecker S, Lopes RD, Massaro T, et al. Antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome treated medically or with percutaneous coronary intervention or undergoing elective percutaneous coronary intervention: Insights from the AUGUSTUS trial. *Circulation* 2019;140:1921-1932.

When patients with atrial fibrillation (AF) undergo percutaneous coronary intervention (PCI), the ideal antithrombic therapy would be an oral anticoagulant and aspirin plus a $P2Y_{12}$ inhibitor. However, such regimens have increased bleeding risk compared to an oral anticoagulant plus a $P2Y_{12}$ inhibitor without aspirin. This so-called dual therapy approach has not been shown to increase ischemic events. Still, the optimal regimen for different subgroups of patients with AF and coronary artery disease (CAD) is unclear.

The AUGUSTUS trial investigators specified three mutually exclusive subgroups to explore the safety and efficacy of antithrombic regimens. The patient subgroups were: acute coronary syndrome (ACS) treated medically, ACS undergoing PCI, and stable CAD undergoing PCI. The antithrombic regimen comparisons used a unique 2 × 2 factorial design wherein apixaban was compared to warfarin and aspirin was compared to placebo in patients taking a $P2Y_{12}$ inhibitor. The primary outcome was major or clinically significant bleeding. Secondary outcomes were death or hospitalization and the composite of death, myocardial infarction (MI), stroke, stent thrombosis, or urgent revascularization. Patients were randomized for up to 14 days after ACS or PCI and treated for six months. From 492 sites in 33 countries, 4,614 patients were randomized, 2,811 with ACS and 1,784 with elective PCI. Among ACS patients, 1,714 were treated by PCI and the rest medically. For the entire cohort, the mean CHA_2DS_2-VASc score was 4, and the mean HAS-BLED score was 3, with no significant differences among the three groups. The apixaban-treated cohort experienced less major bleeding compared to the warfarin cohort in the medically treated ACS patients (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.28-0.68), PCI-treated ACS patients (HR, 0.68; 95% CI, 0.52-0.89), and elective PCI patients (HR, 0.82; 95% CI, 0.64-1.04), but with similar death and ischemic events in all three groups ($P = 0.71$). The authors concluded that in the three subgroups of CAD patients with AF, apixaban plus a $P2Y_{12}$ inhibitor provides superior safety and similar efficacy outcomes as treatment with warfarin, aspirin, or both for six months.

■ COMMENTARY

The authors of this prespecified subgroup analysis of the AUGUSTUS trial used a unique 2 × 2 factorial technique to compare antithrombic regimens in patients taking a $P2Y_{12}$ inhibitor: apixaban vs. warfarin and aspirin vs. placebo. They demonstrated that apixaban plus a $P2Y_{12}$ inhibitor without aspirin was safer and equally efficacious as warfarin, aspirin, or both in ACS patients managed medically and PCI patients with ACS or stable CAD. In comparing apixaban vs. warfarin, the number needed to treat to prevent one significant bleed was 16 for the ACS medical group, 23 for the ACS-PCI group, and 39 for the elective PCI group. Also, the endpoint of death or hospitalization was reduced with apixaban vs. warfarin, with no difference in death or ischemic events across all three patient groups. In comparing aspirin to placebo, the number needed to harm (NNH) with aspirin was 33, 13, and 11 in the three groups, respectively. Further, the death or hospitalization and death or ischemic events endpoints were not different on aspirin vs. placebo. In the two PCI subgroups, the endpoint of stent thrombosis or MI was numerically lower in the aspirin group. However, this was offset by the higher bleeding rate, resulting in no net clinical benefit.

Other recent trials of direct oral anticoagulants (DOAC) vs. warfarin in PCI patients, such as PIONEER AF-PCI (rivaroxaban) and RE-DUAL PCI (dabigatran), also revealed lower bleeding rates with a DOAC plus a $P2Y_{12}$ inhibitor vs. warfarin, $P2Y_{12}$, and aspirin therapy, without an increase in ischemic events. However, it was unclear whether the results were driven by lower doses of DOAC (dabigatran) or the omission of aspirin. This AUGUSTUS trial substudy helps clarify these issues because the authors used the recommended stroke prevention doses of apixaban and employed a unique factorial technique that allowed for comparing aspirin to placebo. Interestingly, in the lower-dose dabigatran arm of RE-DUAL PCI, patients exhibited higher rates of stent thrombosis and MI. This AUGUSTUS data cannot establish the efficacy of not using aspirin in PCI patients, and there may be high-risk subgroups of post-PCI patients in whom triple therapy for some period is warranted.

There were limitations to this analysis. Although the safety of apixaban plus a $P2Y_{12}$ inhibitor therapy in the total trial population was replicated, the subgroups were underpowered for bleeding risk. Also, since patients were randomized for up to 14 days after PCI, many received aspirin during their initial management of ACS. In addition, the study ended at six months after enrollment, so the ideal therapy after six months is unknown. The strongest feature was the inclusion of medically managed ACS patients, which can be up to one-third of all ACS patients. In this group, the NNH on aspirin was 11 vs. 33 in ACS PCI patients. Thus, there may be a stronger case for aspirin in PCI patients, especially those with ACS. Along with other trials, AUGUSTUS suggests that dual antithrombic therapy without aspirin can be considered for six months after PCI or in medically treated ACS patients with AF to reduce bleeding risk. The challenge is identifying PCI patients who are at higher risk of ischemic events and also may need aspirin therapy for some period. ■

ABSTRACT & COMMENTARY

The Safety and Effectiveness of Pyrethroid Insecticides as the Battle Against Mosquitoes Continues

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: There is a statistical association between a urine test suggestive of exposure to pyrethroid insecticides and increased mortality over the subsequent 14 years.

SOURCE: Bao W, Liu B, Simonsen DW, Lehmler HJ. Association between exposure to pyrethroid insecticides and risk of all-cause and cause-specific mortality in the general US adult population. *JAMA Intern Med* 2019; Dec 30. doi: 10.1001/jamainternmed.2019.6019. [Epub ahead of print].

Pyrethroid insecticides are synthetic analogues of permethrin, a naturally occurring insecticide found in chrysanthemum flowers. The synthetic insecticides are more stable with sun exposure than permethrin. Pyrethroids are used widely for pest control, agricultural spraying, prevention of insect infestations on pets, mosquito-bite prevention in humans, and lice treatment. Pyrethroid use is widespread in the United States and, in the era when organophosphates have been deemed dangerous, increasingly common.

Once inhaled or ingested (or absorbed through the skin, although not much gets into the body this way), pyrethroids are metabolized and excreted in the urine. Although pyrethroids generally are considered to be nontoxic in mammals, chronic pyrethroid exposure has been postulated to relate to chronic diseases, including heart disease and diabetes. To better determine the actual relationship between pyrethroid exposure and mortality, Bao et al used data from the National Health and Nutrition Examination Survey (NHANES) to evaluate links between urinary levels of a pyrethroid metabolite, 3-phenoxybenzoic acid (3-PBA) and subsequent death rates. The subject sample used in the study is representative of the adult U.S. population. A total of 2,116 individuals ≥ age 20 years (mean age 43 years) were tested for urine 3-PBA during the years 1999 to 2002. Researchers reviewed mortality data at the end of 2015, giving about 14 years of follow-up.

There were 246 deaths in the study cohort: 41 associated with cardiovascular disease and 52 with cancer. Higher levels of 3-PBA were associated with higher rates of death (8.5%, 10.2%, and 11.9% in the lowest, middle, and highest tertiles of 3-PBA levels, respectively). Controlling for all relevant factors, 3-PBA levels were associated with all-cause mortality and coronary vascular disease mortality, but not with cancer mortality. The authors noted some limitations. First, single urine tests of pyrethroid metabolites might not be indicative of total chronic exposures over time. Second, 3-PBA can be ingested from the environment, without indicating actual exposure to or contact with the original pre-metabolism pyrethroid compounds. Third, only one metabolite was measured, and this might not be relevant to exposure to different pyrethroids used in different regions of the world. Finally, the pyrethroid exposure measured by 3-PBA might merely have been a marker of concurrent exposure to other toxic insecticides and pesticides without the pyrethroid compound being responsible for the identified risk.

■ COMMENTARY

Pyrethroid insecticides are used widely and can be considered to be ubiquitous in the United States. Exposure is not easily avoided.[1] In fact, pyrethroids can be credited with a low risk of West Nile virus and other arthropod-transmitted infections in many urban areas. Before dropping pyrethroids from our armamentarium against West Nile, Zika, dengue, chikungunya, and malaria, we should realize these data are preliminary and, as the authors suggested, in need of replication.

As detailed by Timothy Winegard in the 2019 book *The Mosquito*, mosquitoes have been responsible for the outcomes of many key battles in human history, for the rise and fall of empires and civilizations, and for the shortened lives of leaders, including Alexander the Great.[2] Even around the time of the founding of the United States, mosquito-borne illnesses caused lethal outbreaks in North America. Still, despite medical and public health advances, malaria kills nearly half a million children each year, mostly in sub-Saharan Africa. Controlling mosquitoes and mosquito-transmitted illnesses is important.

From 2000 to 2016, the authors of 61 different epidemiologic studies evaluated health outcomes as

compared to pyrethroid exposures.[3] Unfortunately, none of those studies were uniformly strong, and clear cause-effect relationships between pyrethroid exposure and adverse human health outcomes have not been proven.[3] Helpful lay literature is available to counsel people concerned about pyrethroid safety.[4]

Pyrethroids continue to be a key weapon — if an imperfect one — against mosquitoes. However, the battle rages. Mosquitoes are becoming increasingly resistant to pyrethroids. At least in parts of West Africa, *Anopheles* mosquitoes increasingly express a sensory appendage protein (SAP2) that makes them resistant to the effects of pyrethroids.[5] The expression of this protein increases with exposure to pyrethroids.[5] With concerns spreading for pyrethroid resistance among malaria-transmitting mosquitoes, bednets impregnated with pyrethroids have become less effective since 2015.[6] Host-seeking mosquitoes tend to fly and swoop from above the torso of the potential host.[6] Using added barriers (even including organophosphates) above bednets would provide additional insecticidal activity while keeping the more toxic barrier chemicals beyond the reach of the people (especially children) under the nets.[6] These combined "barrier bednets" have been shown to be effective in Burkina Faso.[6]

Another option is to add a pyrethroid synergist to bednets to make them more effective when mosquitoes develop resistance to pyrethroids. One such agent is piperonyl butoxide, which inhibits the metabolic enzymes in the cytochrome P450 pathway that detoxify pyrethroids. In Cote d'Ivoire, bednets impregnated with both piperonyl butoxide and a pyrethroid were approximately twice as effective in killing *Anopheles* mosquitoes as a standard pyrethroid-impregnated net.[7] Malaria and other mosquito-transmitted infections continue to plague humans in many parts of the world. Pyrethroid insecticides have been helpful in reducing morbidity and mortality from mosquito-borne illnesses, but pyrethroid resistance among mosquitoes is increasing, and legitimate though unproven concerns exist that pyrethroid exposure might increase the risk of human heart disease. Barriers added to conventional pyrethroid-impregnated bednets and combinations of pyrethroids and synergistic agents on bednets might help extend the ability of bednets to protect against malaria. ■

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PHARMACOLOGY UPDATE

Peanut (Arachis hypogaea) Allergen Powder-dnfp (Palforzia)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved the first immunotherapy drug for the mitigation of peanut allergy. The drug is an oral immunotherapy, which represents the first approved therapy for treating any food allergy. Peanut powder oral immunotherapy (POIT) is made from defatted peanut flour and formulated as capsules and sachets.

INDICATIONS

POIT is indicated for the mitigation of allergic reaction, including prophylaxis that may occur with accidental exposure to peanuts.[1] It is approved for use in patients with confirmed diagnosis of peanut allergy. POIT should be used with a peanut-avoidant diet.[1]

DOSAGE

Treatment with POIT is administered in three sequential phases: initial dose escalation, up-dosing, and maintenance.[1] Escalation may start for patients age

4-17 years. Up-dosing and maintenance may continue for patients ≥ 4 years of age. The initial dose escalation involves five daily doses of 0.5 mg, 1 mg, 1.5 mg, 3 mg, and 6 mg (in five blisters). Up-dosing is a 22-week escalation from 3 mg daily to 300 mg daily. The daily maintenance dose is 300 mg daily. Injectable epinephrine should be prescribed. Patients should be observed in a healthcare setting after administration of the initial dose escalation and the first dose of each up-dosing level. Treatment should be discontinued if the patient cannot tolerate doses up to and including the initial 3 mg dose. POIT is available as 0.5 mg, 1 mg, 10 mg, 20 mg, and 100 mg capsules and 300 mg sachets.

POTENTIAL ADVANTAGES

This is the first FDA-approved oral immunotherapy for desensitizing peanut allergy in children to help reduce the risk of allergic reactions.

POTENTIAL DISADVANTAGES

POIT can cause anaphylaxis (9.4% vs. 3.8% for placebo), which can occur at any time during therapy.[1] It should not be given to patients with uncontrolled asthma or a history of eosinophilic esophagitis.[1] The most frequently reported adverse reactions (> 30% vs. placebo) that occurred in the up-dosing phase included

[This is the first FDA-approved oral immunotherapy for desensitizing peanut allergy in children to help reduce the risk of allergic reactions.]

abdominal pain (67% vs. 35%), vomiting (36% vs. 16%), nausea (32% vs. 14%), oral pruritus (31% vs. 10%), throat irritation (40% vs. 17%), cough (32% vs. 23%), and skin pruritus (32% vs. 20%).[1] Overall, 11.6% of subjects in an active group withdrew from a study vs. 2.4% in a placebo group.[2]

The logistics of POIT administration are challenging. These include a 23-week initial and up-dosing period, an observation period during and after initial dose escalation (20-30 minutes), and between the first dose and first dose of each up-dosing level (for at least 60 minutes) under supervision of a healthcare professional. Daily maintenance is required to maintain effect.[1] Powder should be consumed with a meal and delayed after exercise and hot water exposure (shower, bath) and during illness (e.g., viral illness).

COMMENTS

The efficacy of POIT was evaluated in a randomized, double-blind, placebo-controlled study that included 551 subjects with peanut allergy (to ≥ 100 mg of peanut protein) age 4-55 years.[1,2] Subjects were randomized to POIT (n = 416) in an escalating-dose program or placebo (n = 139). The primary endpoint was the percent of subjects who could tolerate a single dose of 600 mg peanut protein in an exit double-blind, placebo-controlled food challenge with no more than mild allergic symptoms after six months of maintenance treatment. Subjects who did not reach 300 mg/day were considered nonresponders. Key secondary endpoints included response rate after a single dose of 300 mg and 1,000 mg of peanut protein.

No statistically significant benefit was observed in subjects age 18-55 years. In the age 4-17 years group (n = 496), response rates for the intent-to-treat (at least one dose of study drug) analysis for 600 mg, 300 mg, and 1,000 mg were 67.2%, 76,6%, and 50.3%, respectively, compared to 4.0%, 8.1%, and 2.4%, respectively, for placebo. For those who completed the study (n = 296 for POIT and n = 116 for placebo), response rates for POIT were 84.5%, 96.3%, and 63.2% compared to 4.3%, 8.6%, and 2.6% for placebo.

An open-label, long-term, safety and tolerability, three-year study is in progress. Completion is expected by December 2024.[3] Peanut sublingual and epicutaneous immunotherapy also has been investigated.[4]

CLINICAL IMPLICATIONS

Approximately 1 million children in the United States are allergic to peanuts, with only 20% outgrowing their allergy.[5] The primary way to avoid severe and potentially life-threatening reactions is strict avoidance. Peanut oral immunotherapy offers an agent to desensitize an individual against accidental exposure up to 1,000 mg in some individuals age 4-17 years. Many allergists offer desensitization therapy with commercially available peanut flour, but POIT is the only FDA-approved treatment. POIT is only available through the Palforzia Risk Evaluation and Mitigation Strategy. The drug costs $890 for a 30-day 300 mg maintenance dose. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. **About what percent of older patients admitted for heart failure exacerbations are on medications known to exacerbate heart failure?**
   a. 10%
   b. 25%
   c. 50%
   d. 65%

2. **Recent studies have shown the enhanced safety, with equal efficacy, of dual antiplatelet therapy without aspirin in patients with atrial fibrillation undergoing percutaneous interventions. A substudy of the AUGUSTUS trial showed similar results in which new clinical group?**
   a. Type 2 diabetes patients
   b. Medically treated acute coronary syndrome patients
   c. Patients with HAS-BLED scores > 4
   d. Patients with CHA_2DS_2-VASc scores > 4

3. **Pyrethroid-impregnated bednets:**
   a. have been directly linked to death from cardiovascular events.
   b. are less effective than in the past due to resistance proteins in mosquitoes.
   c. might be improved by subtracting compounds that alter the metabolism of pyrethroids in mosquitoes.
   d. are no longer considered safe for human use.

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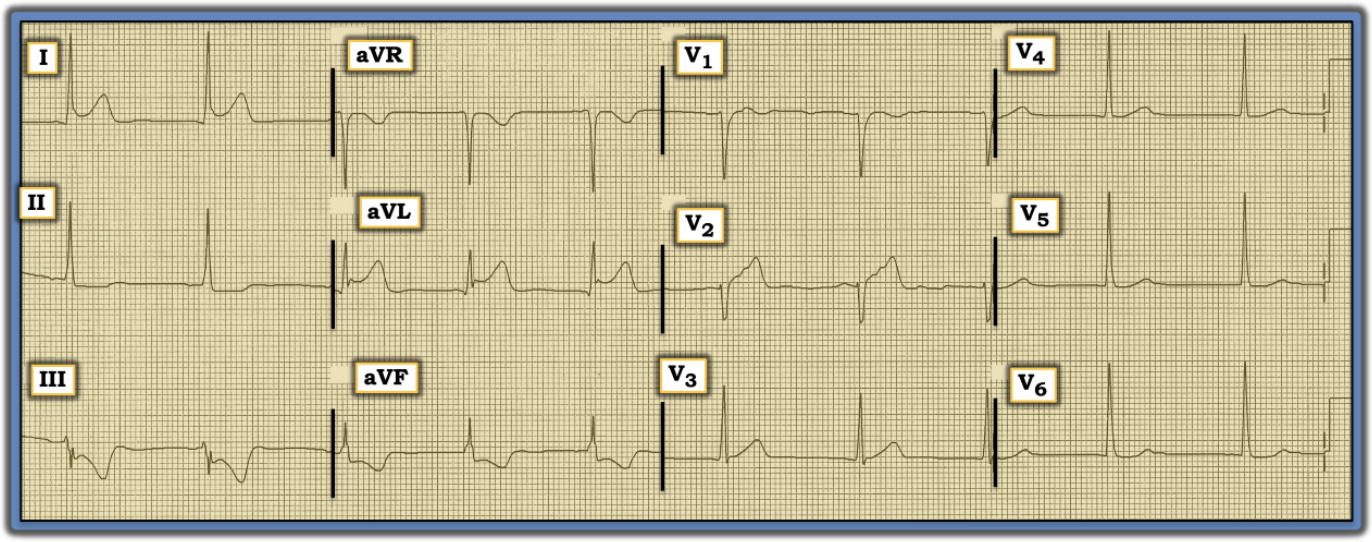
Dr. Grauer reports no financial relationships relevant to this field of study.

A 'Normal' Initial ECG?

The ECG in the figure below was obtained from a 30-year-old man who was admitted to the hospital to "rule out myocardial infarction." His symptoms of chest discomfort were thought to be atypical and unlikely to be due to a cardiac etiology. His initial ECG (not shown) was interpreted as normal. Evaluation, including serial troponins and stress testing, were deemed normal. Before sending the patient home, the ECG in the figure below was obtained.



Although the initial ECG on this patient was reported as normal, this predischarge tracing most certainly is not normal. The patient should not be discharged until further evaluation.

The rhythm in the figure is fairly slow and slightly irregular. Atrial activity is uncertain. Upright P waves are not seen in lead II, so the mechanism of the rhythm is not sinus. The QRS complex is narrow, and the rhythm is slightly irregular. It is hard to determine if ectopic atrial P waves are intermittently present, or if this is a minimally irregular form of atrial fibrillation. But what can be said is the rhythm is supraventricular; therefore, assessment of ST-T wave morphology for potential ischemic change is valid.

The most remarkable ST-T wave abnormalities are seen in the limb leads. There is ST elevation with an upward concavity in leads I and aVL. The most concerning finding is mirror-image opposite ST-T wave depression in lead III. This looks acute. The other two inferior leads (leads II and aVF) also show ST depression. The ST-T wave in lead V2 looks disproportionately tall and potentially hyperacute, given the reduced QRS amplitude in this lead.

We cannot comment on whether the initial ECG was truly normal since we were not shown this initial tracing. What can be said is that regardless of the negative work-up on this patient, the ECG in the figure shows alarming ST-T wave changes in the limb leads. Based on this ECG, the cardiologist decided to perform cardiac catheterization before discharge. Severe narrowing of the left circumflex artery was found, which was stented.

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