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ABSTRACT & COMMENTARY

Atorvastatin: What Is Good for the Heart Is Good for the Kidneys

By Angela Chu, PharmD, BCPS, and Martin S. Lipsky, MD

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Drs. Chu and Lipsky report no financial relationships relevant to this field of study.

SYNOPSIS: For patients at risk of or who already have been diagnosed with cardiovascular disease and are taking atorvastatin, an added benefit is improved kidney function in a dose-dependent manner.

SOURCE: Vogt L, Bangalore S, Fayyad R, et al. Atorvastatin has a dose-dependent beneficial effect on kidney function and associated cardiovascular outcomes: Post hoc analysis of 6 double-blind randomized controlled trials. *J Am Heart Assoc* 2019;8:1-9.

Data from six randomized, controlled trials evaluating patients on atorvastatin for cardiovascular outcomes were pooled and analyzed in this post hoc analysis. Participants were included if they had follow up data of ≥ 12 months; were older than 18 years of age; had more than two serum creatinine values documented; and were assigned to a fixed dose of either placebo, atorvastatin 10 mg, or atorvastatin 80 mg in their respective studies. Patients with known primary renal disease, including end-stage renal disease, were excluded. Participant data were collected from the ASCOT, CARDS, ASPEN, SPARCL, TNT, and SAGE trials.[1-6] A total of 10,057 placebo group patients, 12,763 atorvastatin 10 mg patients, and 7,801 atorvastatin 80 mg patients were studied. From the reciprocal of serum creatinine levels, a slope of kidney function line was calculated and used to evaluate primary and secondary outcomes. This slope linearly correlates to glomerular filtration rates (GFR).

The primary outcome was kidney function decline over time, with slopes of reciprocal serum creatinine (standard deviations) of 0.009 (0.0008), 0.011 (0.0006), and 0.014 (0.0006) mg/dL-1/year for placebo patients, atorvastatin 10 mg patients, and atorvastatin 80 mg patients, respectively ($P < 0.0001$), across all groups.

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One study that included atorvastatin 10 mg vs. 80 mg showed similar dose-dependent renal improvement of 0.012 (0.0007) vs. 0.015 (0.0007) mg/dL-1/year, respectively ($P = 0.0009$).[5] Vogt et al showed that kidney function improves over time, with the greatest improvement seen with a dose of atorvastatin 80 mg.

The secondary outcome was the effect of kidney function on major cardiovascular events, cardiovascular deaths, and all-cause mortality. This study showed statistically significant protective benefits in all secondary outcomes across all three arms. When adjusted for the study, sex, age, body mass index, low-density lipoprotein value, blood pressure, use of concurrent renin-angiotensin-aldosterone system inhibitors, aspirin or diuretics, and history of cardiovascular disease, a protective effect was found in both atorvastatin groups in major cardiovascular events ($P < 0.0001$), cardiovascular death (hazard ratio [HR], 0.92; $P = 0.0367$ in atorvastatin 10 mg and HR, 0.87; $P = 0.0448$ in atorvastatin 80 mg) and all-cause mortality (HR, 0.88; $P < 0.0044$ in atorvastatin 80 mg). Vogt et al showed that improved renal function is associated with improved cardiovascular outcomes, with the greatest benefit seen with atorvastatin 80 mg.

■ COMMENTARY

Statins are among the most commonly used class of medications, and atorvastatin is one of the most frequently prescribed statins.[7] Studies indicate that statins reduce the risk of heart attack, stroke, and death from heart disease by about 25% to 35%.

Recognizing the link between kidney function and cardiovascular disease,[8] Vogt et al speculated whether atorvastatin also might affect kidney function decline. They found that in patients with or at risk of cardiovascular disease, atorvastatin improved kidney function in a dose-dependent manner over time. Even though guidelines differ for treating hyperlipidemia, research suggests that despite the known benefits of statins, there is a significant gap between patients on statins and patients who should be on statins.[9,10] For patients who receive a statin, there also is an inconsistency in intensity of statin prescribed (i.e., patients who are clinically indicated for high-intensity therapy often receive low-intensity therapy).[10] The findings by Vogt et al reveal an additional benefit on kidney function from atorvastatin. Further, it appears high-intensity treatment yields additional benefit over lower-intensity therapy. These findings provide additional motivation for primary care physicians to be more aggressive about adhering to recommendations for statin use. A question that often arises in the minds of primary care physicians is: Are all statins created equal? In the case of kidney function, they may not be. A study comparing the effects of atorvastatin and rosuvastatin on kidney function decline among patients with diabetes revealed that rosuvastatin was associated with a more rapid decline in kidney function.[11] Another study demonstrated that while simvastatin was associated with a decrease in proteinuria, it did not demonstrate a renoprotective effect on GFR.[12] However, this study used mild- to moderate-intensity simvastatin, and it is possible higher-intensity simvastatin therapy might yield a renoprotective effect. Vogt et al noted that the beneficial effects of atorvastatin in their study may not be applicable to all statins. Undoubtedly, as more researchers explore the effects of statins on kidney function, new data will direct the primary care physician about how to optimize statin therapy to help preserve kidney function. ■

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ABSTRACT & COMMENTARY

Reducing Mortality in Stable Ischemic Heart Disease Patients

By Michael H. Crawford, MD

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

SYNOPSIS: A multivariate analysis of a large registry of patients with stable ischemic heart disease revealed that beta-blocker use was associated with lower mortality only when prescribed in the first year after acute myocardial infarction.

SOURCES: Sorbets E, Steg PG, Young R, et al. Beta-blockers, calcium antagonists, and mortality in stable coronary artery disease: An international cohort study. *Eur Heart J* 2019;40:1399-1407.

Nissen SE, Reed GW. Can we trust observational data for clinical decision-making? *Eur Heart J* 2019;40:1408-1410.

The European Society of Cardiology recommends both beta-blockers and calcium channel blockers as first-line treatment for symptomatic patients with stable ischemic heart disease (SIHD). However, there are little data on whether such therapy improves outcomes. In the absence of randomized, controlled trials (RCTs), Sorbets et al examined the association between beta-blockers or calcium channel blockers and clinical outcomes.

Patients were enrolled between November 2009 and June 2010 in 45 countries and followed for five years. The primary outcome was all-cause mortality. Other outcomes included cardiovascular mortality, myocardial infarction, and stroke. Beta-blocker and calcium channel blocker therapy and their doses were ascertained annually. The total study population was 32,378, of which a complete data set was available for 68%. At baseline, 78% of patients were on beta-blockers. Multivariate adjusted hazard ratios (HR) showed no relationship between beta-blockers and any primary or secondary outcome.

In patients ≤ 1 year post-myocardial infarction (MI), beta-blocker use was associated with a lower risk of all-cause mortality (HR, 0.68; 95% confidence interval [CI], 0.50-0.91; $P = 0.01$) and cardiovascular mortality (HR, 0.52; 95% CI, 0.37-0.73; $P = 0.0001$). In patients > 1 year post-MI, there were no differences in outcomes for those on beta-blockers, and there was no difference in outcomes with beta-blockers after categorization by presence of angina. At baseline, 27% of patients were on calcium channel blockers, most of which were long-acting dihydropyridines (80%). There was no association with calcium channel blockers and outcomes. The authors concluded that in a contemporary population of SIHD patients, beta-blocker use was associated only with lower mortality if patients were ≤ 1 year following an acute MI. Calcium channel blocker use was not associated with lower mortality or MI.

■ COMMENTARY

The recommendation to use beta-blockers in almost all SIHD patients is an abstraction from RCTs conducted decades ago in acute MI patients. These trials were performed before the extensive use of reperfusion and revascularization and prior to the widespread use of secondary prevention therapies such as statins. The potential benefits of calcium channel blockers were extrapolated from their demonstrated efficacy for relieving angina and small, randomized, post-MI trials.[1] Considering the absence of RCTs showing a benefit of beta-blockers and calcium channel blockers in SIHD patients, Sorbets et al conceived the prospective, observational CLARIFY study (prospeCtive observational

LongitudinAl RegIstry oF patients with stable coronary arterY disease). Its strengths included its large, international design and the fact that the authors recruited SIHD patients with a spectrum of characteristics from whom data were collected prospectively. Also, this was a contemporary study, with high rates of revascularization and proven secondary prevention therapies. In addition, the authors chose relatively hard endpoints: all-cause and cardiovascular mortality, MI, and stroke. They showed that beta-blockers significantly reduced mortality only in patients who were within one year of an acute MI. Further, their findings suggest calcium channel blockers do not reduce mortality. These results are consistent with those of smaller studies and post hoc analyses of larger trials. Further, a subgroup analysis showed that the results were robust across all subgroups analyzed. Since no harm was discovered, Sorbets et al stated that it was acceptable to use beta-blockers and calcium channel blockers for symptom relief and other indications (e.g., hypertension in SIHD patients), but not as secondary prevention agents.

Sorbets et al, along with Nissen and Reed in an accompanying editorial, noted the study's weaknesses. Like any observational study, there may be residual confounders that were not accounted for in Cox models. The authors did not employ the more rigorous propensity score adjustments. Although patients were enrolled prospectively, the data analysis was not prespecified, so this was essentially a post hoc analysis, which is inherently biased. Also, the study was not blinded, and the outcomes were not adjudicated.

Further, patients were not enrolled at the time of drug initiation, which biases the study toward those who can tolerate the therapy. Finally, patients with clear indications for beta-blockers, such as severe heart failure and life-threatening ventricular arrhythmias, were excluded.

Considering these weaknesses, Nissen and Reed opined that size alone does not guarantee accuracy. They pointed out that the HRs in the study did not meet the more rigorous criteria beyond statistical significance (> 2.0 or < 0.5). Thus, they considered this study only hypothesis-generating. However, since no RCT is likely to be conducted on this issue and considering the consistency of this study with others, I do not plan on recommending beta-blockers purely for secondary prevention in SIHD patients. ■

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ABSTRACT & COMMENTARY

Hot Beverages and Esophageal Cancer

By David Kiefer, MD

Clinical Assistant Professor, Department of Family Medicine, University of Wisconsin; Clinical Assistant Professor of Medicine, Arizona Center for Integrative Medicine, University of Arizona, Tucson

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

SYNOPSIS: In a cohort of more than 50,000 people, there was a higher risk of esophageal squamous cell carcinoma in those who consumed higher quantities of mostly black tea at hotter temperatures.

SOURCE: Islami F, Poustchi H, Pourshams A, et al. A prospective study of tea drinking temperature and risk of esophageal squamous cell carcinoma. *Int J Cancer* 2019; Mar 20. doi: 10.1002/ijc.32220. [Epub ahead of print].

For many of us, warm beverage consumption is an important routine to start our day or stave off the chilling effects of those long winter days. Drinking teas (infusions) and coffee is pan-cultural; rare is the locale lacking in medicinal or culinary hot drinks. With this context, an article title that dampens our enthusiasm for this ritual is eye-catching. The authors of this population-based study in Iran attempted to explore some of the concerns, as cited in their introduction, with regularly exposing our bodies to hot liquids. Other research on this topic has shown a mixture of results, some connections to esophageal cancer, some without an obvious cause-effect (possibly, as the authors hypothesized, due to flaws in data connection, such as recall bias of the study participants regarding their memory of the temperature of the beverages consumed in the past). These uncertainties have led to some ratings of "very hot" (≥ 150° F) beverage drinking as "probably carcinogenic," rather than the more worrisome "carcinogenic."

This prospective study was conducted in one province in Iran, a geographic region with a particularly high rate of esophageal squamous cell carcinoma (ESCC), which previous studies had associated with tea drinking. The authors followed 50,045 adults between the ages of 40 and 75 years through home interviews or phone calls. Research staff conducted interviews to identify ESCC

risk factors and collected data about demographics and nutrition.

Regarding tea drinking, research assistants asked study participants for a subjective analysis of how warm or hot the tea they drink usually is, as well as the time between tea pouring and drinking. In addition, participants were given tea the temperature of which was measured, and they were asked how the tea they normally drink compares to that tea.

Attempts were made to contact participants annually; fewer than 1% have been lost to follow-up. On average, participants were followed for 10.1 years, during which records indicated that 328 cases of esophageal cancer occurred. Of these 328 cases, 11 were adenocarcinoma by pathology; 317 were presumed to be SCC (285 by pathology, 32 considered "likely" cases). Statistics were run on these ESCC cases in the cohort of 50,027 people, and compared to black tea consumption in mL per day (in quintiles) and tea temperature ranges of < 60° C, 60-64° C, and ≥ 65° C. Green tea consumption was low (average 42 mL daily) compared to black tea (more than 1,100 mL daily). Drinkers were split into two groups based on the quantity consumed.

Then, researchers ran the numbers for tea temperature and tea amount. For drinkers of tea (black plus green) cooler than 60° C, it did not matter how much tea they drank; there was no increased ESCC risk. For drinkers of tea ≥ 60° C, higher amounts showed an increased risk.

■ COMMENTARY

In this prospective cohort study that included more than 50,000 people followed over 10 years, Islami et al found that the risk of ESCC was higher for people who drank more beverages that were hot (rather than warm). They pointed to the improvements in their research methodology over past work, namely that an effort was made, through several techniques, to quantify the temperature and amount of the tea consumed in a region of Iran known for both its tea drinking and its incidence of ESCC.

In some respects, the connection between hot beverages and cancer makes sense. The researchers documented the carcinogenic potential that can arise from thermal damage to esophageal tissue or from the formation of carcinogenic compounds. In addition, they described why this might occur only past a certain temperature threshold, perhaps due to damage to the esophageal cells that then permit toxins to lead to DNA damage and oncological change. One class of toxins known to affect people in this area are the polycyclic aromatic hydrocarbons, which enter the human body through diet or cigarette smoking.

Should we counsel our patients to shy away from their favorite tea or coffee? As with other attempts to extrapolate research on one population to other regions or demographics, it is unclear. The most concerning findings here are in those who drank both a lot of tea and at a high temperature (and this was mostly black tea). It probably would be safe to say that if a clinician sees patients who fall into those categories that they would mitigate some of their ESCC risk by moderating both quantity and temperature of the tea consumed. Islami et al did not comment on coffee, nor, for the most part, green tea. The authors' commentary on the possible involvement of toxins, too, is an interesting bent to these results. It makes one branch out from the temperature and quantity of warm/hot beverages to consider plant quality (e.g., contaminant-free sources) in case the carcinogenic transformation involves toxins, too. ■

PHARMACOLOGY UPDATE

Imipenem, Cilastatin, and Relebactam Injection (Recarbrio)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a new antibacterial drug combination for complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). This three-drug combination contains a new beta-lactamase inhibitor, relebactam, and an existing combination of imipenem/cilastatin. Relebactam is the third new beta-lactamase inhibitor after avibactam and vaborbactam. Imipenem/cilastatin and relebactam (IMI/REL) received the FDA's qualified infectious disease product designation, given to products intended to treat

serious or life-threatening infections, and was granted priority review. IML/REL is marketed as Recarbrio.

INDICATION

IMI/REL can be prescribed to treat cUTI, including pyelonephritis caused by these susceptible gram-negative microorganisms: *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Klebsiella aerogenes*, and *Pseudomonas aeruginosa*.[1] IMI/REL also can be prescribed to treat complicated intra-abdominal infections caused by these susceptible gram-negative microorganisms: *Citrobacter freundii*, *E. coli*, *E. cloacae*, *Bacteroides* species (*fragilis*, *caccae*, *ovatus*, *thetaiotaomicron*, *stercoris*, *vulgatus*, *uniformis*), *Klebsiella oxytoca*, *K. aerogenes*, *K. pneumoniae*, *Fusobacterium nucleatum*, *P. aeruginosa*, and *Parabacteroides distasonis*.

DOSAGE

The recommended dose is 1.25 g (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) given by intravenous infusion over 30 minutes every six hours.[1] Dosage should be adjusted based on estimated creatinine clearance. Duration of treatment is four to 14 days based on severity and location of infection. IMI/REL is available as a single-dose vial containing imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg.

POTENTIAL ADVANTAGES

The inhibitions of mainly class A and class C beta-lactamases by relebactam results in a two- to 128-fold reduction in in vitro minimal inhibitory concentrations of various nonsusceptible imipenem gram-negative microorganisms, including *Klebsiella pneumoniae* carbapenemase (KPCs) and serine carbapenemase producers.[2] Relebactam restored activity of imipenem/cilastatin in animal models of infection caused by imipenem-nonsusceptible, KPC-producing Enterobacteriaceae and *P. aeruginosa* (Pseudomonas-derived cephalosporinases).[1]

POTENTIAL DISADVANTAGES

Concomitant use of IMI/REL with ganciclovir, valproic acid, or divalproex is not recommended because of an increased risk for seizures.[1] The safety and efficacy of IMI/REL in patients < 18 years of age have not been established.[1] IML/REL is not active against class B beta-lactamases; it is minimally active against class D beta-lactamases.

COMMENTS

The approval of IMI/REL was supported by previous clinical data regarding the effects of imipenem/cilastatin on cIAI and cUTI.[1,3,4] These Phase II studies showed that IMI/REL was noninferior to imipenem/cilastatin in terms of clinical or microbiological response.[3,4] The contribution of relebactam mainly was based on in vitro and animal infection models. Clinical trials provided limited safety and efficacy data.[1] The authors of a Phase III trial compared IMI/REL and colistimethate sodium against imipenem/cilastatin in the treatment of imipenem-resistant bacterial infections (n = 47).[5] The trial included subjects with hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumoniae (VABP), cIAI, and cUTI. The primary endpoint was the percent with favorable overall response (FOR) up to day 30 (up to nine days after completing study treatment). FOR was defined as: HABP/VABP survival through day 28; cIAI: all pretherapy symptoms of index infection resolved with no evidence of resurgence, no additional treatment (i.e., additional antibiotics, unplanned surgery, or procedures); cUTI: symptom resolution with no additional antibiotics or microbiological response. Percent with FOR was 71.4% for IMI/REL compared to 70.0% for IMI/colistimethate.

CLINICAL IMPLICATIONS

Generally, carbapenem resistance is due to the production of carbapenemases. Relebactam added to imipenem/cilastatin joins ceftazidime/avibactam as beta-lactamase-enhanced antibacterials indicated for cIAI and cUTI and meropenem/vaborbactam for cUTI. The three beta-lactamase inhibitors feature similar overlapping profiles against various beta-lactamase enzymes, particularly KPC-producing carbapenamases.[2] However, there are nuances of activity against different mutations where one may be superior.[6] In addition, the molecular partner is another factor, as imipenem is less likely to be subject to bacterial (e.g., *Pseudomonas*) efflux pumps (a resistance mechanism due to extrusion of the drug from the bacterial cell) than ceftazidime and meropenem.[2,7]

These antibacterials should be reserved only to treat infections that are caused by microorganisms that are proven or strongly suspected to be susceptible to these agents. The cost for IMI/REL was unavailable at the time of this review. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. **In the study by Vogt el al, at what dose did atorvastatin demonstrate the largest benefit on cardiovascular outcomes and all-cause mortality?**
   a. 10 mg
   b. 20 mg
   c. 40 mg
   d. 80 mg

2. **In stable ischemic heart disease patients, beta-blockers for secondary prevention are efficacious in:**
   a. almost all patients.
   b. those within one year of an acute myocardial infarction.
   c. post-stroke patients.
   d. those with heart failure and preserved left ventricular ejection fraction.

3. **Which characteristics of tea consumption in Iran are correlated with a higher risk of squamous cell carcinoma of the esophagus?**
   a. Low temperature tea, but in high quantities
   b. High temperature tea, in low quantities
   c. High temperature tea, in anything but low quantities
   d. There is no correlation between tea consumption and cancer

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

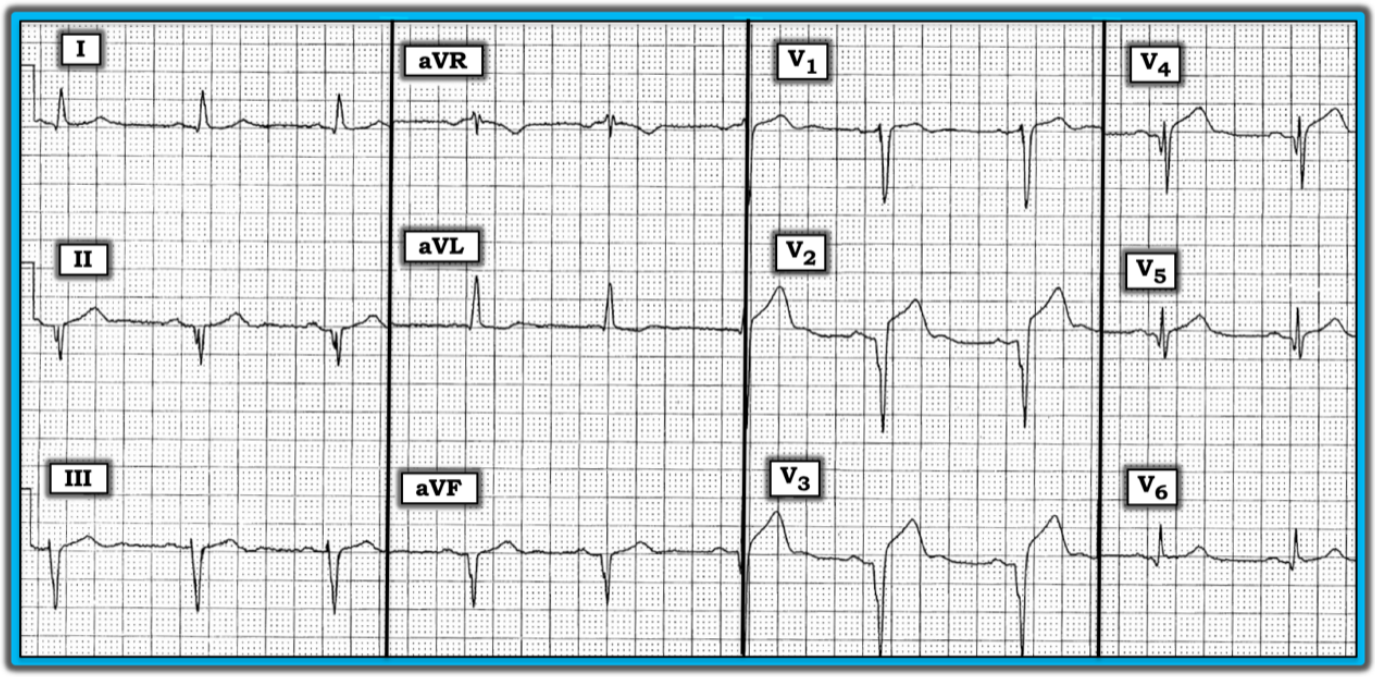
By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

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

Are the Changes New, Recent, or Old?

Imagine examining the ECG in the figure below without any accompanying clinical information. How would one interpret this tracing? What might one suspect is going on?



The rhythm is sinus at 60 beats/minute to 65 beats/minute. The PR, QRS, and QTc intervals are normal. There is marked left axis deviation. There is no chamber enlargement. But the most remarkable ECG findings relate to the assessment of the Q-R-S-T changes.

Large Q waves with fragmentation are visible in leads II and aVF. This strongly suggests there has been inferior myocardial infarction (MI) at some point. Preservation of an initial r wave in lead III suggests that in addition to inferior MI, there is left anterior hemiblock. Lack of ST elevation in any of inferior lead suggests that the inferior MI is old.

In the chest leads, large QS complexes in lead V2 and lead V3, together with Q waves in leads V4, V5, and V6, suggest there has been extensive anterolateral MI. Despite this, preservation of the initial r wave in lead V1 suggests the septum remains intact. There is significant anterior ST elevation. This begins in lead V1, and attains 2-3 mm in leads V2, V3, and V4. Does the anterolateral MI represent acute injury or old infarction? A third possibility might be prior MI with a superimposed new or recent infarction.

Clinical correlation will be needed to determine whether the changes seen in the chest leads represent acute or recent MI (prior MI with superimposed new injury) or longstanding changes of left ventricular (LV) aneurysm that has developed some time after extensive anterolateral MI.

Learning the history is essential. If the patient is experiencing new chest pain, repeating the ECG a short time later may show evolution if an acute event is in progress. Finding a prior ECG would be invaluable for telling if ECG changes in the tracing with this article are new. If the patient is in the hospital or ED, serum troponin should be increased if this is an acute or recent event. Finally, echocardiogram may be helpful if it shows a large LV aneurysm.

The ECG with this article could reflect development of LV aneurysm following a previous extensive anterolateral MI. That said, it is difficult to prove this without additional clinical correlation. For further discussion on and additional information about this case, please visit: http://bit.ly/2YXA8wh.