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ABSTRACT & COMMENTARY

Carbohydrates and Insulin Resistance: Pondering Food Quality vs. Quantity

By Joseph E. Scherger, MD, MPH

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SYNOPSIS: Researchers posit that solving the obesity epidemic is not as simple as eating less and moving more.

SOURCE: Ludwig DS, Aronne LJ, Astrup A, et al. The carbohydrate-insulin model: A physiological perspective on the obesity pandemic. *Am J Clin Nutr* 2021; Sep 13:nqab270. doi: 10.1093/ajcn/nqab270. [Online ahead of print].

Carbohydrates all become sugar in the body and stimulate insulin secretion. Our ancestral diets were relatively low in carbohydrates. Further, those carbohydrates that existed in nature were unrefined and did not raise blood sugar levels quickly like today's processed foods.

Recently, Ludwig et al argued why eating less and moving more is a failed strategy for losing weight and combatting obesity. These conditions are not a matter of energy balance or calories in vs. calories out, what might be referred to as the energy balance model (EBM). Rather, Ludwig et al traced the problem to the types and quality of food consumed through what they called the carbohydrate-insulin model (CIM).[1]

A key part of CIM is glycemic load (GL) and how that affects insulin. Processed grains and foods with high levels of free sugar carry a heavier GL. The authors explained how consuming a high GL diet can trigger a series of physiological events that disrupt normal bodily functions and lead to more insulin resistance, which can cause more fat deposition.

The consequences are devastating to health and results in a long list of chronic diseases. Besides excess weight and obesity, insulin resistance has been connected to fatty liver disease, hypertension, hyperlipidemia, and type 2 diabetes.[2-5]

To put it in simpler terms, Ludwig et al believe the focus should be more on what humans eat — the *quality* of the food consumed — more than *how much* food is consumed. CIM is theoretical, but the authors have provided a framework with hypotheses that can be tested. They called on other investigators to conduct

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more rigorous studies into the EBM vs. CIM, which could lead to progress on this critical public health matter.

■ COMMENTARY

What we eat is more important than the calories we consume. It is hard to move beyond the logic of calories in, calories out for understanding excess weight. In the end, calories do matter.

Carbohydrates drive hunger through fluctuating blood sugar levels. Those who consume processed carbs eat much more in the end. Energy-dense fats and protein foods (e.g., nuts, seeds, eggs, meat, and fish) are much more satisfying and result in less hunger and stable blood sugar levels.

As Ludwig et al and others have hypothesized, time-restricted eating (i.e., consuming meals only during an eight- to 12-hour daytime window) could be important for a healthy metabolism.[6,7] I tell my patients the magic formula for a proper diet is low carbohydrate intake, adequate protein intake, healthy fats, and time-restricted eating (a window no wider than 12 hours daily). ■

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ABSTRACT & COMMENTARY

First-Line Therapy for Hypertension

By Michael H. Crawford, MD

Professor of Medicine, Lucy Stern Chair in Cardiology, University of California, San Francisco

SYNOPSIS: When comparing angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) to treat hypertension, researchers observed no difference in major cardiovascular events — but a better safety profile for ARBs.

SOURCE: Chen R, Suchard MA, Krumholz HM, et al. Comparative first-line effectiveness and safety of ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers: A multinational cohort study. *Hypertension* 2021;78:591-603.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are class I evidence A first-line agents for treatment initiation in hypertension. However, little is known about their comparative effectiveness and safety. Chen et al compared the effectiveness and safety of ACEIs and ARBs for the first-line treatment of hypertension in a global network of eight large observational databases. They used statistical and informatics approaches to reduce confounding and bias.

They generated more than 6 million effect estimates for 55 outcomes comparing all recommended first-line antihypertensives. At least 2,500 patients treated with each drug class met the inclusion/exclusion criteria from 1996 to 2018. Inclusion meant patients treated with one agent, either an ACEI or an ARB, for one year during a period when both agents were available. The authors excluded patients who were exposed to any other antihypertensive either before or within seven days of starting an ACEI or ARB. Four of the 55 outcomes studied

were the primary effectiveness outcomes: acute myocardial infarction (AMI), heart failure (HF), stroke, and a composite of these three (plus sudden cardiac death). The 51 secondary outcomes were safety outcomes or adverse effects based on the product labels, including angioedema, cough, hypotension, syncope, and electrolyte abnormalities. For the main on-treatment analysis, continuous exposure to the drug was required. Propensity score models were used to adjust for comorbidities and other covariates. Also, to further adjust for residual bias, 76 negative control outcomes were analyzed. Finally, sensitivity analyses, including measured blood pressure (BP), were employed. A total of 2,297,881 patients were started on an ACEI and 673,938 were started on an ARB (48% vs. 15%).

After more than 500 days of follow-up, there was no difference between those started on ACEI and ARB in the primary clinical outcomes, which was not changed by sensitivity analysis. The secondary outcomes showed significantly higher incidences of pancreatitis (HR, 1.32), angioedema (HR, 3.31), cough (HR, 1.32), gastrointestinal (GI) bleed (HR, 1.18), and abnormal weight loss (HR, 1.18) on ACEI vs. ARBs. After a Bonferroni correction, only cough and angioedema remained statistically significant. The authors concluded that although the safety profile for ARBs was better for the first-line treatment of hypertension, these drugs were not more effective at preventing major cardiovascular events.

■ COMMENTARY

This report takes observational studies to a new level — or, if you prefer, to the big data level. By amassing eight large observational databases, Chen et al studied more than 3 million patients undergoing initial drug therapy for hypertension with ACEI and ARBs. The results support many clinicians' current approach: Start ARBs rather than ACEIs because of the difference in safety. The name of the game in hypertension treatment is adherence, as this is a chronic condition that usually does not cause symptoms. Many clinicians have realized cough associated with ACEI often is enough to sabotage medication compliance. Once ARBs became generic, I abandoned ACEI for the treatment of hypertension for this reason.

Chen et al found another issue with ACEI: angioedema, which is less common than cough but much more serious. Also concerning was the higher incidence of pancreatitis and more GI bleeding cases with ACEI, although these did not survive the Bonferroni correction ($P < 0.01$ vs. $P < 0.05$). However, pancreatitis in this instance may be caused by edema of the pancreatic duct, which can occur with excess bradykinin. ACEIs retard the degradation of bradykinin, which is thought to explain cough and angioedema. GI bleeding is a new adverse effect that has not been reported.

There were limitations to this study, besides its observational nature and the potential for residual confounding and bias. It is not possible to evaluate differences between different drugs in each class. However, most patients in the ACEI arm were treated with lisinopril, which also is the most commonly prescribed antihypertensive. Thus, this study reflects the real-world use of drug therapy for hypertension. In addition, specific drug use one week after initiating first-line therapy was not considered, so some patients may have been prescribed other agents later. In fact, this is highly likely, as most hypertensive patients require more than one drug to control their BP. Despite these drawbacks, this is the largest study to compare the two drug classes for first-line therapy of hypertension. The results favor the preferential use of ARBs rather than ACEIs when initiating treatment for hypertension. ■

ABSTRACT & COMMENTARY

Adjuvanted Zoster Vaccine: Persistent Protection

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The adjuvanted recombinant zoster vaccine efficacy is high and persistent, with apparent plateauing at > 84% four to six years after vaccination.

SOURCE: Boutry C, Hastie A, Diez-Domingo J, et al. The adjuvanted recombinant zoster vaccine confers long-term protection against herpes zoster: Interim results of an extension study of the pivotal Phase III clinical trials (ZOE-50 and ZOE-70). *Clin Infect Dis* 2021; Jul 20:ciab629. doi: 10.1093/cid/ciab629.

Boutry et al reported the interim results of a follow-up study of adults older than age 50 years enrolled in two pivotal trials (ZOE-50/70) that demonstrated efficacy in the prevention of herpes zoster in adults by administration of a glycoprotein E-based adjuvanted recombinant vaccine (Shingrix). Patients participating in

that study were offered, after approximately five years, entry into this long-term follow-up evaluation, and 7,413 of the original cohort of 14,648 agreed to do so. Vaccine efficacy during the follow-up period, approximately 5.1 to 7.1 years post-vaccination, was 84.0% (95% CI, 75.9-89.8), with an incidence of 8.6 per 1,000 patient-years. The overall efficacy through the entire period after vaccination was 90.9% (95% CI, 88.2-93.2). A plateau of more than 84% efficacy was reached between post-vaccination years 4 and 6. Antibody levels and T cell measures also plateaued at approximately sixfold above prevaccination levels at years 5 to 6.

■ COMMENTARY

As pointed out by the authors, Zostavax had lower levels of efficacy than seen with Shingrix in clinical trials and its efficacy diminished rapidly over time. In fact, any efficacy demonstrated with Zostavax was not statistically significant eight years after vaccination of individuals > 60 years of age. In contrast, Shingrix not only provides higher levels of protection, but its efficacy appears to have plateaued at > 84% at four to six years after vaccination.

The follow-up data of Shingrix indicates protection provided is long-lasting and, in fact, modeling of its immunological results suggests the measured responses will persist for at least 20 years post-vaccination. However, it must be recognized that immune correlates of protection remain uncertain. Of importance, though, is that immunosuppressive and immune-modulating therapies were not allowed during the study. ■

ABSTRACT & COMMENTARY

Progression of Coronary Calcium on Statin Treatment

By Michael H. Crawford, MD

Professor of Medicine, Lucy Stern Chair in Cardiology, University of California, San Francisco

SYNOPSIS: In those treated with statins vs. those who were not, statins decreased plaque volume in plaques with little or no calcium (plaque regression) and increased calcium density without changes in plaque volume in calcified plaques (plaque stabilization).

SOURCE: van Rosendael AR, van den Hoogen IJ, Gianni U, et al. Association of statin treatment with progression of coronary atherosclerotic plaque composition. *JAMA Cardiol* 2021; Aug 18:e213055. doi: 10.1001/jamacardio.2021.3055. [Online ahead of print].

Statin therapy has been associated with lower levels of lipid-rich coronary plaque and an increase in calcification, but high plaque burden is associated with a high future risk of coronary events. To explore whether higher calcium density associated with statin use results in a lower risk of coronary events, investigators from 13 sites in seven countries enrolled 2,252 consecutive patients with suspected or known coronary artery disease (CAD) from 2013 to 2016.

For this cohort study, the authors excluded those with uninterpretable studies, those without lesions, those who stopped or initiated statins after a baseline coronary CT angiography (CCTA), and those with no information on statin use. The remaining 857 patients formed the study cohort (63% men; mean age, 62 years). The baseline and follow-up CCTAs were read blinded in a core lab. Any plaques detected were categorized by plaque volume and composition based on fixed thresholds of Hounsfield Units (HU). The main outcome was progression of the composition of each individual plaque. The progression or regression of the plaques according to statin use was determined by changes in plaque volume.

To evaluate the association between statin therapy and coronary calcium density, van Rosendael et al excluded low-density and fibro-fatty plaques. Researchers analyzed 2,458 plaques in the baseline and follow-up CCTAs. Continuous statin use was present in 64% of the cohort. In the untreated group, plaque volume increased for all compositional types. Statin therapy was associated with decreased plaque volume in low attenuation plaques and fibro-fatty plaques, but not in the calcified plaques. Considering the calcium plaques alone, statin therapy was not associated with a change in plaque volume, but rather a transformation to denser calcium. Also, an interaction analysis of baseline plaque volume and calcium density showed denser plaques were associated with slower plaque progression. The authors concluded statin use was associated with greater rates of transformation to high-density calcified coronary plaque, and there was slower plaque progression with increasing calcium density levels.

■ COMMENTARY

The authors believe this study provides insight into the reduction in coronary events when statins are deployed as secondary prevention in patients with known or suspected CAD. However, coronary event outcomes were not assessed, so this is conjecture. On the other hand, this study expands on their previous publication from this cohort, an examination of patients who

experienced an acute coronary event after their first CCTA vs. a matched group that had not. In that work, the authors showed acute coronary syndrome patients had significantly less highly calcified plaques (> 1,000 HU).[1] In this most recent analysis, statin therapy seemed to reduce the size of fibro-fatty and low attenuation (very little calcium) plaques, but increased the calcium density of calcified plaques. These findings imply statins are shrinking the lipid core of plaques, shrinking the non-calcified plaques, and increasing the calcium density of calcified plaques, both of which should reduce coronary events.

There were limitations. This was an observational study. Statin use was not randomized but determined by the patient's physician. Thus, it is not surprising the two groups were significantly different in several characteristics. The statin group was older, included more men, and included more patients with diabetes and hypertension. Although the authors adjusted for it in the multivariate analyses, unmeasured confounders could be present. Also, the decision to prescribe statins may have excluded both low-risk patients (no indication) and high-risk patients who were excluded from the study. In addition, the interval between CCTA exams was determined clinically, not by protocol. Finally, lesions that had coalesced or occluded between exams were not evaluated, which further limits the generalizability of the results.

Despite these limitations, the results do add to our knowledge about the effects of statins on coronary plaques and probably explain the paradox of increasing calcium scores on serial CCTAs in the face of fewer clinical events. This is of clinical importance because it supports the advice not to repeat CCTAs in patients with high calcium scores who were started on statins because they likely will be higher. This will cause anxiety in patients and does not inform therapy, as this likely is a good sign of plaque stabilization. ■

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PHARMACOLOGY UPDATE

Atogepant Tablets (Qulipta)

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.

The FDA has approved a second non-injectable calcitonin gene-related peptide (CGRP) receptor antagonist to prevent episodic migraine in adults. Atogepant is an orally administered, small-molecule solution similar to rimegepant (Nurtec ODT), which the FDA approved in February 2021 for acute treatment and in May 2021 as preventive treatment of episodic migraine. The FDA granted atogepant tablets priority review. It is distributed as Qulipta.

INDICATIONS

Atogepant can be prescribed to prevent episodic migraine in adults.[1]

DOSAGE

The recommended dose is 10 mg, 30 mg, or 60 mg taken orally once daily with or without food.[1] The 10 mg dose is recommended for patients on a strong CYP3A4 inhibitor, with severe renal impairment, or with end-stage renal disease (creatinine clearance < 30 mL/min). Patients taking an organic anion transport protein inhibitor should be on 10 mg or 30 mg of atogepant. The dose should be 30 mg or 60 mg for those on strong and moderate CYP3A4 inducers. Atogepant is available as 10 mg, 30 mg, and 60 mg tablets.

POTENTIAL ADVANTAGES

Atogepant provides an alternative orally administered, preventive treatment instead of monthly subcutaneous injections (e.g., erenumab, galcanezumab), an every-three-month subcutaneous injection (e.g., fremanezumab), or intravenous infusion every three months (e.g., eptinezumab).

POTENTIAL DISADVANTAGES

Atogepant requires daily dosing, with potential for inconsistent adherence, while monoclonal antibodies are given monthly up to every three months. The most commonly reported adverse reactions (vs. placebo) were nausea (5%-6% vs. 3%), constipation (6% vs. 1%), and fatigue/somnolence (4%-6% vs. 3%).[1] Atogepant is an oral tablet, while rimegepant can be taken orally or sublingually.

COMMENTS

The efficacy of atogepant was evaluated in two randomized, double-blind, placebo-controlled, 12-week studies. Study 1 (n = 910) and study 2 (n = 629) were conducted in subjects who reported about eight migraine days per month, with a range of four to 14 days.[1-3] Participants were mainly female (87%-89%) and white (76%-83%).

Subjects were permitted to use acute headache treatment, except for those drugs that act on the CGRP pathway (e.g., gepants). Subjects with cardiovascular risk (e.g., myocardial infarction, stroke, or transient ischemic attacks) were excluded.

In study 1, subjects were randomized 1:1:1:1 to atogepant 10 mg, 30 mg, 60 mg, or placebo. In study 2, randomization was 2:1:2:2 placebo, 10 mg, 30 mg, and 60 mg, respectively. The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) across the 12-week treatment period. Study 1 also included some secondary endpoints that included ≥ 50% MMD responders across 12 weeks, health outcomes (Activity Impairment in Migraine-Diary [AIM-D]) that assesses performance of daily activities (PDA) and physical impairment (PI), and the Migraine-Specific Quality of Life Questionnaire (MSQ).

The MMD declined from a baseline of 3.7 days for the 10 mg dose, 3.9 days for 30 mg, and 4.2 days for 60 mg vs. -2.5 days for placebo ($P < 0.001$ for all comparisons to placebo). Benefit was observed in weeks 1 to 4. The percentages of those demonstrating a 50% or greater response were 56% for 10 mg, 59% for 30 mg, and 61% for 60 mg vs. 29% for placebo. Significant improvement was demonstrated for MSQ for all three doses, and significant improvements in AIM-D domain and PI Domain were seen for 30 mg and 60 mg only. For study 2, MMD reductions from baseline were four days for the 10 mg dose, 3.8 days for the 30 mg dose, and 3.6 days for the 60 mg dose vs. 2.8 days for placebo.

CLINICAL IMPLICATIONS

Migraine is a common disorder, with a worldwide prevalence of 14.4%.[4] CGRP has become a popular target for preventive treatment of migraines. Atogepant is the second non-injectable CGRP available for such treatment after rimegepant. There are no direct comparisons between the two small-molecule receptor antagonists. An indirect transitive comparison between placebo-controlled atogepant and rimegepant clinical trials with similar subject demographics and study design suggested possible differences in efficacy in favor of atogepant. Difference from placebo in MMD ranged from -1.2 days to -1.7 days for atogepant across 12 weeks vs. -0.8 days for rimegepant.[1,5] Responders with ≥ 50% improvement ranged from 56%-61% for atogepant (29% for placebo; $P < 0.001$) vs. 49.1% for rimegepant (41.5% for placebo; $P = 0.044$). There are three monoclonal antibodies (eptinezumab, galcanezumab, fremanezumab) that target the CGRP ligand, and one (erenumab) that targets the CGRP receptor.

A meta-analysis of results from randomized, controlled trials of the erenumab, fremanezumab, and galcanezumab suggests similar effectiveness and safety.[6] After three treatment cycles (12 weeks), the overall MMD difference between treatment and placebo was -1.80 days.[6] Atogepant offers a new oral therapeutic option for prevention of episodic migraine in adults. The cost for a 30-day supply is $991. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. **Which statement is true about successful long-term weight management?**
   a. Limit the consumption of sugary drinks to two per day.
   b. Low-fat diets are the most effective.
   c. Diets loaded with protein are the most sustainable.
   d. Low-carbohydrate diets reduce insulin resistance.

2. **Which is correct regarding the results of administration of Shingrix 5.1 to 7.1 years post-vaccination?**
   a. Its protective efficacy fell within the range of 25% to 50%.
   b. Its protective efficacy fell within the range of 50% to 75%.
   c. Its protective efficacy fell within the range of 75% to 95%.
   d. Its protective efficacy fell within the range of 95% to 99%.

3. **A comparison of angiotensin-converting enzyme inhibitors (ACEI) vs. angiotensin II receptor blockers for first-line monotherapy in hypertension demonstrated an increased incidence of:**
   a. acute myocardial infarction on ACEI.
   b. heart failure on ACEI.
   c. stroke on ACEI.
   d. angioedema on ACEI.

4. **Statin therapy in patients with atherosclerotic coronary artery plaques compared to no statin therapy results in:**
   a. increased plaque volume and decreased calcium.
   b. reduced plaque volume of fibro-fatty plaques.
   c. reduced calcium density of calcified plaques.
   d. no difference.

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.

[IN FUTURE ISSUES]

How Meat Consumption Affects Mental Health

Age Considerations and Chronic Kidney Disease

Internal Medicine [ALERT]

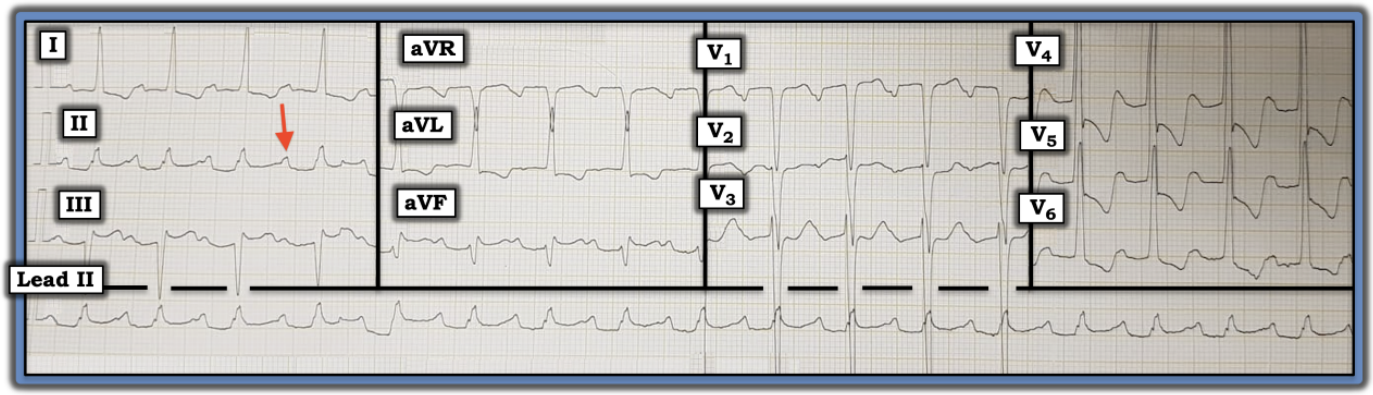
ECG Review

By Ken Grauer, MD

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

What Is the 'Bix Rule?'

The ECG in the figure below was obtained from a middle-aged man with a history of exertional chest pain and dyspnea. How would one interpret this tracing? Does the red arrow in lead II show a sinus P wave?



The red arrow in the figure was thought to be a sinus P wave. Instead, it probably is just one of two P waves that appear within each R-R interval. Normally, the PR interval shortens as the heart rate increases. As a result, it is unusual to see first-degree AV block with sinus tachycardia. Instead, recognition of atrial activity with a long PR interval in a patient with tachycardia (as is seen in the figure) should prompt consideration that a second P wave for each R-R interval may be "hiding" within each QRS complex. Awareness of this probability is known as the "Bix Rule." This made me strongly suspect the rhythm in the figure was not sinus tachycardia with first-degree AV block, but rather atrial tachycardia with 2:1 block.

In support of my suspicion is the finding of subtle notching on the upstroke of the R wave in lead II, as well as an r' deflection at the end of the QRS complex that I thought might represent a second P wave in leads III and aVF. Most of the time, distinction between sinus tachycardia and atrial tachycardia with 2:1 block can be determined by further monitoring. If the rhythm is sinus tachycardia, then the rate of the rhythm should slow as the patient's clinical condition improves. It almost always will become clear within a short period there is only a single P wave for each QRS complex.

Elsewhere, although the QRS complex appears to be slightly widened (i.e., slightly more than half a large box in duration), it does not appear to be wide enough for complete left bundle branch block (LBBB), which requires QRS prolongation to at least 0.12 seconds. Instead, I suspected a combination of left ventricular hypertrophy (LVH) and incomplete LBBB, both of which may account for slight QRS widening.

Also, note there is marked increase in QRS amplitude, with significant "overlap" of R waves and/or S waves in most chest leads. As a result, despite up to 4 mm of ST depression in lead V4 (with significant ST depression also in lateral leads V5 and V6), this amount of ST depression probably is not disproportionate, considering the tremendous increase in QRS amplitude we see in most chest leads. As a result, I attributed the lateral lead ST depression to the combination of LVH and incomplete LBBB, not to ischemia.

I suspect the rhythm in the figure is atrial tachycardia with 2:1 block. In addition, there is marked LVH with LV "strain" and probable incomplete LBBB, but I thought it likely that there were no acute ST-T wave changes. Clinical correlation, further evaluation, and close follow-up will be needed to verify my impression.

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