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ABSTRACT & COMMENTARY

COVID-19 Vaccination: The Heart of the Matter

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford

SYNOPSIS: The occurrence of myocarditis after receipt of COVID-19 vaccines is most frequent in young men and generally benign, with rapid resolution only through supportive care. Careful analysis indicates the benefit of vaccination outweighs the risk in all groups for whom the vaccine is recommended.

SOURCE: Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:977-982.

From December 2020, when the FDA issued emergency use authorizations for Moderna and Pfizer-BioNTech COVID-19 vaccines, through June 11, 2021, approximately 296 million doses were administered in the United States, including 52 million doses given to individuals 12-29 years of age. Within that interval, beginning Dec. 29, 1,226 reports of post-vaccination myocarditis were reported to the Vaccine Adverse Event Reporting System (VAERS). The median age of those reported was 26 years (range, 12-94 years), with a median onset three days after vaccination. Most were age 30 years and male.

Investigators performed further review of 323 patients who met CDC definitions for myocarditis, pericarditis, or myopericarditis. All but 4% of these were hospitalized. The median age was 19 years, and 291 of the 323 were men. The median interval between vaccination and onset was two days (range, 0-40 days), with 92% experiencing onset within seven days. The clinical course was mild, with no deaths and with 95% discharged from the hospital at the time of review.

For males age 12-29 years, the myocarditis reporting rate occurring within seven days of a second vaccine dose was 40.6 per million, while it was 2.4 per million for males > age 30 years. The rates for women in these age groups were 4.2 and 1 per million, respectively. The groups with the highest rates were males age 12-17 years (62.8 per million) and males age 18-24 years (50.5 per million).

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After an analysis, researchers concluded the benefits associated with the prevention of COVID-19 outweighed the risk of myocarditis in all groups for whom vaccination has been recommended. Focusing on males age 12-29 years, receiving both vaccine doses was associated with 39-47 cases of myocarditis but with prevention of 11,000 COVID-19 cases, 560 hospitalizations, 138 ICU admissions, and six deaths. This analysis did not take into account the prevention of "long COVID."

■ COMMENTARY

Numerous case reports and small case series describing myocarditis after COVID-19 vaccination are appearing in the literature, and these attest to the usual apparent benign nature of this complication. As one example, Marshall et al reported seven cases in adolescents. All recorded elevated cardiac troponin levels, and all had late enhancement of MRI images with gadolinium enhancement, a characteristic finding in myocarditis.[1] All patients recovered rapidly without apparent sequelae.

Montgomery et al described 23 cases of myocarditis identified within the U.S. Military Health System that occurred over a period during which more than 2.8 million mRNA vaccine doses had been administered.[2] All were male and their median age was 25 years (range, 20-51 years). All recorded elevated serum troponin, and MRI findings were consistent with myocarditis in all eight patients in whom this study was performed. Their illnesses were mild, and all had recovered or were recovering at the time the report was submitted for publication.

The benign nature of the illness described in these series is consistent with the CDC report and conclusions. As they indicate, it will be important that follow-up of these cases continues to assure the absence of any longer-term adverse effects. ■

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ABSTRACT & COMMENTARY

Statins, Cognitive Decline, and Dementia

By Michael H. Crawford, MD

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

SYNOPSIS: An analysis of the ASPREE database showed that with almost five years of follow-up, statins are not associated with cognitive decline or dementia in a large group of elderly subjects in whom multiple tests of cognition were performed serially.

SOURCE: Zhou Z, Ryan J, Ernst ME, et al. Effect of statin therapy on cognitive decline and incident dementia in older adults. *J Am Coll Cardiol* 2021;77:3145-3156.

There is little evidence supporting a connection between taking statins and experiencing cognitive decline and dementia. Zhou et al analyzed the systematically collected comprehensive cognitive data in the Aspirin in Reducing Events in the Elderly (ASPREE) trial to determine the association of statin use with incident dementia and mild cognitive impairment (MCI), to assess the influence of statin lipophilicity on neurocognitive effects, and to identify factors that may modify statin effects on cognition. ASPREE was a large prospective, randomized, placebo-controlled study of daily low-dose aspirin in subjects > age 70 years or > age 65 years in U.S. minorities. Subjects presented with no prior cardiovascular (CV) disease events or dementia and scored > 78 on the Modified Mini-Mental State Examination (3MS). Investigators recruited participants between 2010 and 2014 in

Australia and the United States. Taking a closer look at ASPREE, Zhou et al grouped subjects by their baseline statin use, resulting in 12,948 not on statins and 5,898 on statins for closer examination. The mean age was 74 years, and 56% were women. More subjects in the statin group were diabetic or hypertensive and were on more concomitant medications. Cognitive function was assessed at baseline; at one, three, and five years; and after the final visit (maximum seven years). Multiple covariates were assessed that could affect neurocognitive function or could interact with statins.

During the median follow-up of 4.7 years, Zhou et al identified 566 cases of dementia. Using statins was not associated with the risk of dementia (HR, 1.16; 95% CI, 0.97-1.40; *P* = not significant). MCI developed in 380 subjects and also was not associated with statin use (HR, 1.44; 95% CI, 0.90-2.29; *P* = not significant). Although statin users recorded lower global cognition scores at baseline, there was no significant difference between statin users and no use of statins groups over the follow-up period.

There were no differences in outcomes among those using lipophilic vs. hydrophilic statins. There were interactions between baseline cognitive scores and statin therapy for the development of dementia. No other interaction effects were found, including baseline LDL cholesterol levels. In addition, sensitivity analyses of the various comorbidities did not alter the results. The authors concluded that in older adults, there was no association between statin use and the development of MCI or dementia.

■ COMMENTARY

In 2012, the FDA issued a warning indicating statins had been recorded in their adverse events reporting system as causing short-term cognitive impairment.[1] This caused quite a stir, and it was hard to convince older patients to take statins. Since then, other investigators reviewed the evidence on which the FDA based its decision, drawing different conclusions.[2-4]

ASPREE focused on patients > age 65 years who completed several cognitive function tests over about five years. Also, the outcomes were adjudicated by a committee, sensitivity analyses were conducted, and researchers explored whether lipophilicity of the statin was of importance. Zhou et al showed statin use was not associated with incident MCI or dementia or that cognitive function declines over time on statins. In addition, they did not find that lipophilicity influenced the results, and sensitivity analyses did not show that comorbidities affected the results. However, in those in the lowest quartile of normal cognitive function at baseline, there was an interaction suggesting a potential statin effect on dementia risk. For this reason, the investigators urged caution in interpreting their data until randomized, controlled trials in progress are completed.

There were other weaknesses to the Zhou et al study. It was a post-hoc analysis of an observational study conducted for other reasons, so there could be residual confounding. There could be an indication bias since the statin group exhibited more CV disease at baseline. Reverse causality is another consideration as declining cognition within the normal range could have been an indication for statins to prevent any CV components to cognitive dysfunction. Also, these were highly selected subjects with few comorbidities, less frailty, and who were taking fewer drugs than an older general population would have been. In addition, there were no data on LDL cholesterol levels, dosage of the statins, and the length of statin use before the study. Finally, this was a relatively short-term investigation.

The main issue is whether the risk of statins outweighs the benefits for older patients. In this regard, some believe heart failure outweighs CV events in older subjects, making statin use more problematic. Since their introduction, the adverse effects of statins have been of great interest. The most serious, rhabdomyolysis, is rare. Early on, liver function was a concern, but routine testing of liver function is no longer recommended since serious liver disease also is rare. There seems to be a real association with diabetes, but it is believed the benefits of statins outweigh this small risk. Muscle symptoms have become the biggest reason patients quit taking statins, but recent controlled studies have shown most of these symptoms are not reproducible. There has been fear that too low cholesterol levels could adversely affect the nervous system, but studies of the PCSK9 inhibitors, which can lower LDL cholesterol to < 20 mg/dL, have not borne this out. Thus, cognitive dysfunction is the new big worry with statins.

The Zhou et al study is reassuring in that over five years, no significant deterioration in cognitive function was observed in a higher-risk elderly population studied serially by multiple cognition tests. ■

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ABSTRACT & COMMENTARY

No Harm in a Morning Cup of Joe

By Martin S. Lipsky, MD

Chancellor, South Jordan Campus, Roseman University of Health Sciences, South Jordan, UT

SYNOPSIS: Habitual coffee consumption was inversely associated with a lower risk of cardiac arrythmia.

SOURCE: Kim EJ, Hoffmann TJ, Nah G, et al. Coffee consumption and incident tachyarrhythmias: Reported behavior, Mendelian randomization, and their interactions. *JAMA Intern Med* 2021; Jul 19:e213616. doi: 10.1001/jamainternmed.2021.3616. [Online ahead of print].

Coffee is one of the most widely consumed beverages; in the United States, close to two-thirds of people drink about three cups per day.[1] Over the last decade, research indicating coffee may offer health benefits continues to accumulate, with evidence linking coffee consumption to lower risks for Parkinson's disease, diabetes, cancer, and even overall mortality.[2-5] On the other hand, some professional societies recommend limiting coffee because of its presumed risk of increasing cardiac arrythmia despite little evidence.[6,7]

To investigate the association of coffee and arrythmias, Kim et al used the UK Biobank, a database of more than 500,000 individuals who completed questionnaires, underwent physical exams, and provided biological samples. After applying exclusion criteria, they assessed 386,258 individuals with a mean age of 56 years and followed them over 3.1 years. Using the outcome measures of tachyarrhythmias (atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia, premature atrial complexes, and premature ventricular complexes), Kim et al found that after adjusting for demographic variables, comorbid conditions, and lifestyle habits, there was a 3% lower risk of incident arrythmia for each additional cup of coffee consumed. The authors also stratified individuals by polygenic profiles related to caffeine metabolism and did not identify an association between genetically differing rates of caffeine metabolism and the risk of arrythmia. Researchers concluded more coffee consumption was associated with a lower risk of arrythmia. Genetically mediated caffeine metabolism did not affect that association.

■ COMMENTARY

First, let me acknowledge my bias. I am addicted to coffee, and the smell in the morning is one of life's joys. However, I always worried about coffee's harmful effects. I am old enough to remember when coffee was linked to pancreatic cancer, an association further research refuted.[8,9] Subsequently, more evidence began accumulating, indicating that rather than harm, coffee consumption might be beneficial, presumably because of its anti-inflammatory and antioxidant effects. Still, concern about caffeine and heart arrythmias persisted, and advising those with palpitations to reduce coffee intake or switch to decaf was common practice. Now, Kim et al have provided reassurance for coffee drinkers: caffeinated coffee does not increase the risk for cardiac arrythmias. Surprisingly, the authors found more coffee consumption was associated with a lower risk of arrythmias. Their findings match other studies, which failed to connect caffeinated beverage consumption with cardiac ectopy.[10]

While premature to urge patients with cardiac arrythmias to start drinking coffee, this work does provide reassurance to those patients who enjoy their morning cup: such consumption is unlikely to be the cause of an arrythmia. For the millions of individuals who suffer from arrythmias and who love coffee, this is great news. ■

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ABSTRACT & COMMENTARY

Anticoagulation Plus Antiplatelet Therapy in Chronic Atherosclerosis

By Michael H. Crawford, MD

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

SYNOPSIS: An analysis of the COMPASS trial for the secondary endpoint of mortality showed the combination of low-dose rivaroxaban and aspirin significantly lowered the all-cause mortality rate vs. low-dose aspirin alone.

SOURCE: Eikelboom JW, Bhatt DL, Fox KAA, et al. Mortality benefit of rivaroxaban plus aspirin in patients with chronic coronary or peripheral artery disease. *J Am Coll Cardiol* 2021;78:14-23.

The Cardiovascular Outcomes for People Using Anticoagulant Strategies (COMPASS) trial compared rivaroxaban 2.5 mg twice a day plus aspirin 100 mg/day (RA group) to aspirin alone (AA group) in patients with known coronary or peripheral vascular disease. The combined primary endpoint was cardiovascular (CV) death, stroke, or myocardial infarction (MI). After 1,323 events, the trial ended early because of favorable outcomes in the RA group.

Subsequently, it was approved for this secondary prevention goal in more than 100 countries, including the United States. The components of the combined primary endpoint constituted the three secondary endpoints of the trial. One was mortality, both all-cause and CV. COMPASS mortality and the factors that influenced mortality were the subject of this report by Eikelboom et al. Mortality was classified as CV when no other clear cause of death was discovered. The potential risk factors for death considered were the extent of polyvascular disease, chronic kidney disease (estimated GFR less than 60 mL/minute), mild to moderate heart failure (EF > 30% or New York Heart Association class I or II), and diabetes.

There were 18,278 patients enrolled in COMPASS at 602 sites in 33 countries who were followed for a mean of 23 months. All-cause mortality was reduced significantly (1.8 for RA vs. 2.2% for AA; HR, 0.82; 95% CI, 0.71-0.96; $P = 0.01$). CV mortality was reduced by 18% in the RA group compared to the AA group (3.4% vs. 4.1%, respectively; HR, 0.82; 95% CI, 0.71-0.96; $P = 0.01$). Coronary heart disease mortality was reduced (0.5% for RA vs. 0.7% for AA; HR, 0.73; 95% CI, 0.55-0.96; $P = 0.03$). There was no appreciable effect on non-CV mortality (1.7% for RA vs. 1.9% for AA; HR, 0.87; 95% CI, 0.71-1.08; $P = 0.20$).

When analyzing specific causes of death, there was no observed effect on non-cerebral bleeding, MI, stroke, heart failure, or sudden death. The overall number needed to treat (NNT) to prevent one death in 30 months was 81. Patient subgroups with risk factors that reduced this NNT included chronic kidney disease (NNT = 59), diabetes (NNT = 53), polyvascular disease (NNT = 47), and heart failure (NNT = 23). In those with more than one of these risk factors, the more that were present the lower the NNT: two risk factors (NNT = 40); three risk factors (NNT = 19). The authors concluded the combination of low-dose rivaroxaban and aspirin vs. low-dose aspirin alone reduced all-cause mortality, mainly because of significant reductions in CV mortality. The authors also observed that the magnitude of the mortality benefit was greater in patients at the highest risk for a CV event.

■ COMMENTARY

The combined endpoint of mortality, stroke, and MI in the overall COMPASS trial was reduced by 24% in the RA group compared to the AA group. The secondary endpoint analysis by Eikelboom et al demonstrated this was caused mainly by a reduction in CV mortality since non-CV mortality was not affected. This reduction in CV mortality coincided with a decrease in all CV events except stroke and heart failure death. This lack of effect on heart failure death is not surprising since heart failure deaths probably are caused by arrhythmias or pump failure. These would not be expected to be influenced by rivaroxaban or aspirin. Cerebral vascular disease probably caused stroke deaths in these patients, not atrial fibrillation.

Also of interest is the fact rivaroxaban alone was not superior to aspirin in COMPASS. This suggests ischemic events drive the reduction in CV mortality. The finding that higher-risk patients benefitted more from the rivaroxaban/aspirin combination suggests patients with more advanced disease are those in whom plaque rupture more likely would result in thrombus formation. Whereas in patients with milder disease, antiplatelet drugs would be sufficient, and the higher risk of an anticoagulant would not result in net clinical benefit.

In the overall COMPASS trial, major bleeding was more common in the RA group compared to the

AA group, but intracranial hemorrhage and fatal bleeding were not. Also, in the mortality analysis by Eikelboom et al, fatal bleeding other than that caused by hemorrhagic stroke was rare and not different between the RA and AA groups. Although rarely fatal, major bleeding is a concern of patients and physicians. This represents a major obstacle to recommending RA for secondary prevention. The message of the Eikelboom et al analysis is patients with demonstrated atherosclerosis and two or more risk factors for a CV event are those who should be targeted for RA therapy. The authors believe the mortality benefit they have shown should tip the equilibrium between benefits and risks. ■

PHARMACOLOGY UPDATE

Insulin Glargine-yfgn Injection (Semglee)

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 the first biosimilar and interchangeable insulin. The agency approved insulin glargine-yfgn as a biosimilar to insulin glargine (Lantus) in June 2020. Now, the manufacturer has provided additional data to meet the criteria for interchangeability. Insulin glargine-yfgn is distributed as Semglee.

INDICATIONS

Insulin glargine-yfgn can be prescribed to improve glycemic control in pediatric and adult patients with type 1 diabetes mellitus and in adult patients with type 2 diabetes.[1]

DOSAGE

The dose is individualized based on blood glucose monitoring, type of diabetes, metabolic needs, prior insulin use, and glycemic control.[1] The drug can be administered one time per day at the same time every day into the deltoid, thigh, or abdomen. Rotate injection sites to lower the risk of localized cutaneous amyloidosis and lipodystrophy. The starting dose in type 1 diabetes patients should be about one-third of total daily insulin requirement. To satisfy the remainder of the daily insulin requirement, use short-acting premeal insulin.[1] For patients with type 2 diabetes who are insulin-naïve, start at 0.2 units/kg or up to 10 units one time per day.[1] Insulin glargine-yfgn is available as 3 mL single patient use prefilled pens and 100 units/mL in 10 mL multiple-dose vials.

POTENTIAL ADVANTAGES

Insulin glargine-yfgn is a cheaper version of Lantus. As an interchangeable biosimilar, it may be substituted at the pharmacy for the reference product without the need for the healthcare provider to intervene, similar to an FDA-approved generic drug.[2]

POTENTIAL DISADVANTAGES

There are no known clinical disadvantages.

COMMENTS

Biosimilar products labeled interchangeable can produce similar clinical results as the reference product. In terms of diminished efficacy or safety of switching between the product and the reference, the risk is not higher than the risk of using the reference product without switching or alternation.[3]

The labeling for insulin glargine-yfgn essentially is identical to Lantus, per FDA guidance.[3] It incorporates the same clinical data that supported the agency's finding of effectiveness and safety of the reference product. The FDA requires switching study or studies to demonstrate interchangeability.[4] The agency recommends not including a description of data from clinical studies conducted to support a demonstration of interchangeability on interchangeable biosimilar labels.[3]

CLINICAL IMPLICATIONS

Insulin glargine-yfgn represents the first biosimilar to be granted interchangeable status and marks an important step for the FDA in supporting a competitive marketplace for biologics. It will be available at a significantly lower cost than Lantus ($98.65 for a 10 mL vial of U-100) vs. $283.56. For five 3 mL pens, the cost is $147.98 vs. $425.31. ■

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CME QUESTIONS

1. **Coffee consumption is associated with a lower risk of:**
   a. cardiac arrythmia.
   b. stroke.
   c. pancreatic cancer.
   d. high cholesterol.

2. **The health benefits of coffee are most likely attributed to:**
   a. caffeine.
   b. bronchodilation.
   c. an antioxidant effect.
   d. a diuretic effect.

3. **Which is correct regarding myocarditis occurring after administration of an mRNA COVID-19 vaccine?**
   a. The median age of its occurrence in recipients was 8 years.
   b. The median interval between vaccination and onset of symptoms was nine days.
   c. The mortality rate is 17%.
   d. The highest incidence occurred in males 12-17 years of age.

4. **In the COMPASS trial mortality analysis, the risk factor associated with the lowest number needed to treat to prevent one death using rivaroxaban plus aspirin vs. aspirin alone in vascular disease patients was:**
   a. diabetes.
   b. polyvascular disease.
   c. heart failure.
   d. all three factors combined.

5. **Which factor likely increases the risk of cognitive decline with long-term statin use?**
   a. Very low baseline cognitive function
   b. Use of lipophilic statins
   c. Higher baseline LDL cholesterol levels
   d. Multiple comorbidities

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.

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Fermented Foods Help the Immune System, Alleviate Inflammation

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Internal Medicine [ALERT]

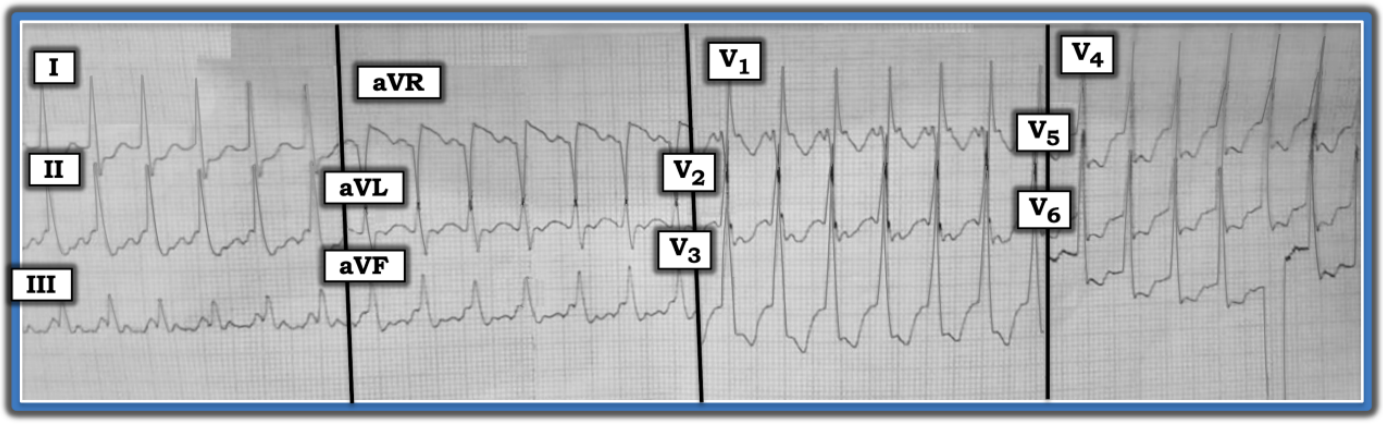
ECG Review

By Ken Grauer, MD

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

Is This Ventricular Tachycardia?

The ECG in the figure below was obtained from an elderly man with chest pain and shortness of breath. Is the rhythm ventricular tachycardia (VT)?



The ECG in the figure shows a regular wide complex tachycardia (WCT) rhythm at a rate of ~150 beats/minute. Sinus P waves are absent because there is no clearly upright P wave in lead II. The small upright deflection seen just before the QRS complex in lead V1 is too close to the QRS complex to be a P wave.

The differential diagnosis of a regular WCT rhythm without sinus P waves includes: VT, supraventricular tachycardia with either aberrant conduction or preexisting bundle branch block, or something else (e.g., a Wolff-Parkinson-White-related arrhythmia or a toxic effect, such as hyperkalemia).

Statistically, the overwhelming majority of WCT rhythms without sinus P waves will turn out to be VT. This is especially true in older individuals with underlying heart disease, in whom 90% or more of the regular WCT rhythms without sinus P waves are the result of VT.

Despite these statistics, I thought the rhythm in the figure was more likely to be supraventricular. QRS morphology is completely typical for right bundle branch block (RBBB) conduction. This is because there is a triphasic (rSR') complex in lead V1, with the S wave descending below the baseline, and with a characteristic slender and taller terminal R' complex. In addition, lateral leads I and V6 both manifest tall, slender R waves with terminal S waves. This specific pattern of QRS morphology for RBBB conduction in leads I, V1, and V6 is highly predictive of a supraventricular etiology.

There appears to be two to one atrial activity in several leads. This atrial activity is best seen in the form of two equally spaced, upright notches within each R-R interval in lead III; two rounded negative deflections within each R-R interval in leads II and aVF; and notching at the very end and very beginning of the QRS complex in lead V1.

Since the ventricular rate is ~150 beats/minute and there are two equally spaced atrial deflections, the QRS would be 150 × 2 = 300 beats/minute. The only rhythm that produces regular atrial activity at this fast of a rate is atrial flutter.

I thought the arrhythmia in the figure was most likely to be atrial flutter with two to one AV conduction. This patient was treated with beta-blockers, which resulted in successful conversion to sinus rhythm. The post-conversion tracing showed sinus P waves with an identical-looking QRS complex, which confirmed that the reason for QRS widening in the figure was preexisting RBBB.

For more information about and further discussion of this case, please visit: https://bit.ly/35g1zC9.