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ABSTRACT & COMMENTARY

Elderly May Not Benefit From Statins for Primary Prevention

By David Fiore, MD

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

SYNOPSIS: In an examination of the data from the much-publicized Systolic Blood Pressure Intervention Trial (SPRINT), the author found no benefit of statin therapy for primary prevention of cardiovascular events or all-cause mortality.

SOURCE: Huesch MD. Association of baseline statin use among older adults without clinical cardiovascular disease in the SPRINT trial. *JAMA Intern Med* 2018 Jan 22. doi: 10.1001/jamainternmed.2017.7844. [Epub ahead of print].

One of the most remarkable advances in cardiovascular medicine must be the use of statin drugs to lower cardiovascular risks. In previous studies, statin therapy has been shown to lower the relative risk of cardiovascular events consistently by approximately 20-25%. However, these studies were not designed specifically to assess elderly subjects.

Huesch attempted to re-examine the data of the widely discussed Systolic Blood Pressure Intervention Trial (SPRINT), looking only at those > 70 years of age (or 65 years of age for the sensitivity analysis). SPRINT, which was published in 2015, was designed to compare intensive vs. standard blood pressure control in non-diabetic patients with increased cardiovascular risk.[1] Approximately one-third of the participants in SPRINT were > 70 years of age (3,054 of 9,361). Of these, 1,350 were taking a statin at baseline. Huesch did not find any statistically significant differences in primary endpoint between the patients on a statin vs. those who were not.

Unfortunately, there were significant differences between those on a statin at baseline and those who were not. Among these differences, those on a statin were more likely to be male, have chronic kidney

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disease, present with a higher body mass index, register higher glucose readings, and demonstrate lower Framingham risk scores. Adjusting for these factors, Huesch still did not find any statistically significant differences in outcomes based on prior statin use.

■ COMMENTARY

Sadly, this analysis does not leave us with a definite answer as to whether we should recommend statin therapy for primary prevention in the elderly. Although the population was large and part of a carefully crafted study, this is a secondary analysis of a non-randomized intervention. The results and conclusions are consistent with another post hoc analysis, this one of the Lipid-Lowering Trial, which was a component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.[2]

On the other hand, as Huesch noted, the authors of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and the Heart Outcomes Prevention Evaluation (HOPE) trials found a benefit from treating the elderly with statins.[3,4] The authors of various review articles and meta-analyses also have touted a benefit of statin treatment in the elderly.[5-7]

Such investigators tended to find some benefit in preventing cardiovascular events but not mortality. Furthermore, their analyses typically included more "young elderly" (65-75 years of age) than very elderly (> 75 years of age). To add confusion to this subject, the Atherosclerotic Cardiovascular Disease Risk Calculator, released in 2017 by the American College of Cardiology/American Heart Association, excludes patients > 79 years of age.

As the U.S. population continues to age and experiences more comorbid illnesses, the question of when to add or remove therapy becomes increasingly urgent. Unfortunately, this study may just add to our confusion, and we may need to wait until the results of the Australian STAtin Therapy for Reducing Events in the Elderly (STAREE) study are released to get a definitive answer. Even then, it is likely that the "answer" won't be so definitive. What do we do in the meantime? We know that cardiovascular events increase as one ages and that statins can lower the risk of these events. What we don't know is when the harm of another medication outweighs the benefits. Furthermore, there seem to be some elderly patients who, despite their elevated lipids, remain free of cardiac disease.

Therefore, a rational approach may be to: 1) use caution when starting statin therapy for primary prevention in the elderly (especially those > 75 years of age); 2) consider stopping statin therapy in the very elderly if they have never experienced a cardiac event; and 3) consider using a calcium score to determine whether to continue statin therapy for primary prevention in those between 65 and 79 years of age, although this approach is not based on study data. ■

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ABSTRACT & COMMENTARY

Stroke Risk in Atrial Fibrillation: A Moving Target?

By Michael H. Crawford, MD

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

SYNOPSIS: An investigation of patients in a national database with atrial fibrillation, no comorbidities, and not on aspirin or anticoagulants showed that the clinical features that make up the CHA_2DS_2-VASc score change over time and can increase a patient's risk for stroke, which could affect therapy decisions. Thus, the CHA_2DS_2-VASc score should be reassessed periodically and appropriate therapeutic actions taken promptly.

SOURCES: Chao TF, Lip GYH, Liu CJ, et al. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;71:122-132.

Gage BF. Stroke prediction rules in atrial fibrillation. *J Am Coll Cardiol* 2018;71:133-134.

The authors of previous studies of stroke risk in patients with atrial fibrillation (AF) have assessed the risk factors imbedded in the CHA_2DS_2-VASc score at baseline and then observed the patients during years of follow up. However, as these patients age, comorbidities that affect their risk often change.

Investigators from Taiwan hypothesized that changes in the CHA_2DS_2-VASc score would carry greater predictive value than the baseline score. From the Taiwan National Health Insurance database, 31,039 patients with AF who were not on antiplatelet or anticoagulant drugs and did not exhibit any features in the CHA_2DS_2-VASc scheme (except age and sex) were identified from 1996-2009. In this group, 4,103 experienced a stroke during follow-up. The follow-up CHA_2DS_2-VASc score was the highest measured before the occurrence of stroke, mortality, or the end of 2009. The difference between the baseline and follow-up CHA_2DS_2-VASc score (delta) and the slope of the score change were calculated.

During follow-up, the mean age increased from 64 to 68 years and the delta CHA_2DS_2-VASc was 1.02. The baseline, follow-up, and delta CHA_2DS_2-VASc scores were higher in those who experienced a stroke. About 52% of patients acquired a new comorbidity that affected the CHA_2DS_2-VASc score, most commonly hypertension (37%), heart failure (27%), and diabetes (13%). CHA_2DS_2-VASc remained unchanged in only 41% of patients. The delta CHA_2DS_2-VASc score predicted stroke (hazard ratio, 1.52; 95% confidence interval, 1.48-1.56; $P < 0.001$) and performed better than baseline or follow-up CHA_2DS_2-VASc. The area under the receiver operating curve (AUC) was 0.74 for delta CHA_2DS_2-VASc, compared to 0.58 for baseline and 0.73 for follow-up. Also, the slope of the delta CHA_2DS_2-VASc was higher in those with stroke compared to those without (0.58 vs. 0.42; $P < 0.001$).

The authors concluded that the CHA_2DS_2-VASc score is not static over time and most patients with AF develop one or more new comorbidities that affect the CHA_2DS_2-VASc score in addition to aging. This increment in the CHA_2DS_2-VASc score also was highly predictive of stroke.

■ COMMENTARY

In some ways, the results of this study are obvious. If one acquires risk factors for stroke over time, the risk of stroke increases. Since this has not been investigated or proven, this study is of interest. The main finding of the study is that the AUC of the follow-up CHA_2DS_2-VASc score is significantly higher than that of the baseline score (0.74 vs. 0.58). However, considering that at baseline all patients included in this study exhibited no comorbidities and registered CHA_2DS_2-VASc scores of 0 for men and 1 for women, this, too, is unsurprising. One would expect that as patients with AF age they would pick up comorbidities that affect the CHA_2DS_2-VASc score, as most subjects in this study did. What is perhaps the most interesting finding in this study is that soon after an increase in the CHA_2DS_2-VASc score, the risk of stroke is higher than later. The editorialist for this article suggested that this is because new comorbidities may not be well controlled early after diagnosis. He noted that the risk of stroke is high early after a transient ischemic attack but decreases over time. The same may be true for newly diagnosed hypertension, heart failure, or diabetes.

There are limitation to this study. It was an insurance database study, and all diagnoses were made by the patient's own physicians. However, the authors

noted that the accuracy of this approach has been validated previously in the Taiwan database. There are no laboratory data available, so the influence of biomarkers cannot be ascertained. Although they assessed the value of changes in the CHA_2DS_2-VASc score, the authors explicitly stated that they are not proposing a new measure of delta CHA_2DS_2-VASc. The authors only showed these data to bolster their point that changes in the CHA_2DS_2-VASc over time must be considered and therapeutic changes made as appropriate to reduce the rising risk of stroke. ■

BRIEF REPORT

After Myocardial Infarction, Increased Risk for Ischemic Stroke Persists for 12 Weeks

By Matthew E. Fink, MD

Louis and Gertrude Feil Professor and Chairman, Department of Neurology, and Assistant Dean of Clinical Affairs, Weill Cornell Medical College; Neurologist-in-Chief, New York Presbyterian Hospital

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

SOURCE: Merkler AE, Diaz I, Murthy SB, et al. Duration of heightened stroke risk after acute myocardial infarction. *Stroke* 2018;49:A172.

Merkler et al performed a retrospective cohort study using inpatient and outpatient claims data from 2008 through 2015 from a nationally representative 5% sample of Medicare beneficiaries ≥ 66 years of age. Diagnosis of acute myocardial infarction (MI) and ischemic stroke were ascertained using validated ICD-9 diagnosis codes. Strokes were included only if they occurred after discharge from the acute MI hospitalization to make sure that periprocedural strokes related to coronary interventions were excluded. Cox regression models were used to sort the groups and perform the analyses, and risk of ischemic stroke was adjusted for demographics, stroke risk factors, and other comorbidities. Survival probabilities were used to compute a hazard ratio for each four-week interval after discharge from the hospital following acute MI. Among 1,746,476 beneficiaries, 46,182 were hospitalized for acute MI and 80,466 were hospitalized for ischemic stroke. Compared to patients without acute MI, patients with stroke and acute MI were older and carried more stroke risk factors. After adjusting for demographics, risk factors, and comorbidities, the risk of ischemic stroke was highest in the first four weeks after discharge from the MI hospitalization (hazard ratio [HR] = 2.7) and remained elevated substantially during weeks five to eight (HR = 2.0) and weeks nine to 12 (HR = 1.6) and no longer was elevated significantly after 12 weeks. Established stroke classification systems categorize MI-associated stroke as occurring in the 30-day period following MI. This study establishes that the elevated short-term risk of stroke extends beyond 30 days and remains elevated for up to 12 weeks following acute MI. ■

PHARMACOLOGY UPDATE

Ibalizumab-uiyk Injection (Trogarzo)

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

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

The FDA has approved a new treatment for HIV-infected individuals who have failed available therapies. Ibalizumab-uiyk is a humanized IgG4 monoclonal antibody produced in murine myeloma cells that acts as a CD4-directed post-attachment HIV-1 inhibitor without affecting CD4 function.[1] This blocks the entry of the HIV-1 virus particles into the host cell, preventing viral transmission. It is the first drug in a new class, differing from previous drugs considered as entry inhibitors, including

enfuvirtide and maraviroc. The FDA designated ibalizumab-uiyk as breakthrough therapy and assigned it orphan status and priority review.[2] It is marketed as Trogarzo.

INDICATIONS

Ibalizumab-uiyk, in combination with other antiretrovirals, is indicated for the treatment of HIV-1 in heavily treatment-experienced adults with multidrug-resistant HIV infections failing their current regimens.[1]

DOSAGE

The recommended dose is a loading dose of 2,000 mg, given intravenously, followed by a maintenance dose of 800 mg every two weeks. Ibalizumab-uiyk is available as a 200 mg (150 mg/mL) single-dose vial.

POTENTIAL ADVANTAGES

Ibalizumab-uiyk provides an option for salvage therapy in patients with multidrug resistance. It is active against HIV-1 that is resistant to all approved antiretroviral agents and demonstrates a long half-life, permitting dosing every two weeks.[1]

POTENTIAL DISADVANTAGES

Decreased susceptibility after multiple administrations has been reported in some patients.[1] Ibalizumab-uiyk requires intravenous administration by a trained medical professional every 14 days. Primary resistance is estimated at approximately 10%.[3] Immune reconstitution inflammatory syndrome has been reported in one subject who was treated with ibalizumab.[1]

COMMENTS

The safety and efficacy of ibalizumab-uiyk was evaluated in a single-arm study in 40 heavily treatment-experienced HIV-1-infected subjects with multidrug resistance.[1] Subjects were required to exhibit a viral load > 1,000 copies/mL, with documented resistance to at least one drug from each of three classes of antiretroviral drugs (NRTI, NNRTI, and PI). Subjects also had to be treated for at least six months and were failing or had recently failed therapy. Many subjects (53%) were treated with ≥ 10 antiretroviral drugs.

The study was comprised of three periods. The first was a control period (day 0-6) when subjects were monitored to established baseline HIV viral load as they stayed on their current failing therapy or on no therapy if they discontinued therapy. In the second period (day 7-13), all subjects received the loading dose on day 7, and those on failing regimens continued that failing course. During the last period (day 14-week 25), viral load was assessed; thereafter, the background regimen was optimized to include at least one drug (investigation drugs were allowed) to which the subject's virus was susceptible. Maintenance dose of ibalizumab-uiyk was started on day 14 and administered every two weeks through the end of the study. The primary endpoint was the proportion of subjects achieving a viral load ≥ 0.5 $\log_{10}$ reduction at the end of the second period compared to the proportion after the first period.

The results were 83% compared to 3%. At Week 25, 50% of subjects demonstrated viral load < 200 copies/mL and 43% < 50 copies/mL. Those with a baseline viral load of ≤ 100,000 copies/mL were more likely to achieve levels < 50 mL (49% vs. 14%) and 48% exhibited a ≥ 2 $\log_{10}$ reduction. The most frequent (≥ 5%) adverse reactions were diarrhea (8%), dizziness (8%), nausea (5%), rash (5%), increase in creatinine levels (10%), increase in bilirubin and lipase levels (5%), and decrease in leukocytes and neutrophils levels (5%).

CLINICAL IMPLICATIONS

HIV-1 features a high mutation rate, which allows the virus to rapidly generate new variants, leading to development of antiretroviral resistance.[4] HIV/AIDS guidelines recommend that in patients who experience treatment drug resistance or treatment failure, a new regimen (preferably three fully active agents and possibly those with a novel mechanism of action) should be sought based on the patient's antiretroviral therapy history and current and past drug resistance testing history.[5] For some highly treatment-experienced patients with extensive drug resistance, maximal virologic suppression may not be possible. Options for these patients would be enrollment in a clinical trial of investigation agents. Ibalizumab-uiyk provides an option with a new mode of action for these patients. The cost for ibalizumab-uiyk is $2,270 for a 2,000 mg single-dose vial. ■

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Clinical Briefs

By Louis Kuritzky, MD

Comparing GLP-1 Agonists

SOURCE: Ahmann AJ, et al. *Diabetes Care* 2018;41:258-266.

There are more similarities than differences among the seven currently available glucagon-like peptide-1 (GLP-1) receptor agonists. The most recently FDA-approved GLP-1 receptor agonist, once-weekly semaglutide (Ozempic), was compared in a head-to-head trial to once-weekly exenatide-ER (Bydureon). In this open-label trial, adult subjects with type 2 diabetes (n = 813) taking one or more oral agents were randomized to receive either 1 mg/week of semaglutide or 2 mg/week of exenatide-ER. Subjects taking semaglutide underwent a titration from 0.25 mg/week for four weeks, then 0.5 mg/week for four weeks, and then 1.0 mg/week for the remainder of the trial; exenatide-ER subjects were started on 2.0 mg/week and maintained that dose throughout the trial. Baseline A1c was 8.3% in the exenatide group and 8.4% in the semaglutide group.

At the conclusion of the trial (56 weeks), the clinically meaningful differences in outcomes were the following: A1c was reduced by 1.5% with semaglutide vs. 0.9% with exenatide; weight declined 5.6 kg with semaglutide vs. 1.9 kg with exenatide; the fraction of subjects attaining an A1c < 7.0% was significantly greater with semaglutide (67% vs. 40%). While gastrointestinal adverse events were more common in the semaglutide treatment arm, injection site reactions were more frequent with exenatide. The efficacy advantages of semaglutide over exenatide-ER were both clinically meaningful and statistically significant. Generally, liraglutide has been regarded as the most potent GLP-1 receptor agonist. It will be interesting to see if semaglutide ultimately bests liraglutide, since both agents have demonstrated favorable cardiovascular outcomes in cardiovascular safety trials. ■

Rivaroxaban vs. Aspirin for Prevention of VTE

SOURCE: Anderson DR, et al. *N Engl J Med* 2018;378:699-707.

The combined benefits of improved efficacy and convenience of direct oral anticoagulants (i.e., apixaban, dabigatran, edoxaban, rivaroxaban) in the setting of atrial fibrillation makes them a preferred choice. For chronic anticoagulation subsequent to recurrent deep vein thrombosis or pulmonary embolism, direct oral anticoagulants are similarly attractive when compared to warfarin.

Might direct oral coagulants offer some advantage for extended venous thromboembolism (VTE) thromboprophylaxis in patients undergoing knee or hip arthroplasty who are known to suffer an increased risk of VTE in the immediate postoperative period?

Anderson et al performed a double-blind, randomized, controlled trial of knee and hip arthroplasty patients. After a run-in period of rivaroxaban 10 mg daily through postoperative day five, subjects were randomized to either continue rivaroxaban or switch from rivaroxaban to aspirin (81 mg/d). This additional VTE thromboprophylaxis continued for nine days post-knee arthroplasty (hence, 14 days total thromboprophylaxis) and 30 days post-hip arthroplasty (hence, 35 days total thromboprophylaxis).

VTE events were rare in both groups (< 1%), and there was no statistically significant difference in VTE events between aspirin and rivaroxaban, nor was there any significant difference in rates of bleeding. For now, aspirin should remain the postoperative choice for extended prophylaxis after knee and hip arthroplasty. ■

Inhaled Corticosteroids and Fracture Risk

SOURCE: Gonzalez AV, et al. *Chest* 2018;153:321-328.

Clinicians have long been reassured by reports about the safety of inhaled corticosteroids (ICS) in asthma, which assert no long-term increased fracture risk, albeit a measurable decrement in bone mineral density (BMD) may be seen. On the other hand, most of the asthmatic population is comprised of younger patients who are not near the peak age of fracture risk. The potential consequences of ICS might be better demonstrated in persons with COPD, who are typically older than the asthma population. In addition, COPD itself is a risk factor for osteoporosis, as is cigarette smoking.

Using the large database of the Quebec healthcare system, fracture rates were assessed in a cohort of 240,110 subjects. Over a five-year follow-up period, more than 19,000 fractures occurred. The mean age of patients with a fracture and the comparison control group was 75 years. Use of ICS for more than four years at a dose of ≥ 1,000 fluticasone equivalents/day was associated with a small but statistically significant 10% increase in relative risk (RR) for hip or upper extremity fracture (RR, 1.10; 95% confidence interval, 1.02-1.19). There did not appear to be any differential risk between men and women. Clinicians should strive to use the minimum ICS necessary to achieve symptomatic improvements in COPD patients. ■

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CME QUESTIONS

1. **Which of the following is a true statement about statin therapy in the elderly?**
   a. It has been shown to cause more harm than benefit.
   b. It has been shown to be beneficial for primary prevention.
   c. There is debate about the balance of harms and benefits, especially for primary prevention.
   d. It should never be prescribed in patients > 79 years of age.

2. **Which of the following is most correct concerning the use of the CHA_2DS_2-VASc score in patients with atrial fibrillation?**
   a. It is guideline-recommended for determining antithrombic therapy in atrial fibrillation.
   b. It should be remeasured if comorbidities change.
   c. New comorbidities should be controlled quickly.
   d. All of the above

3. **Risk of ischemic stroke is increased for 30 days following acute myocardial infarction.**
   a. True
   b. False

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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]

Mefloquine: Still Effective and Safe for Malaria Chemoprophylaxis

Pre-existing Health Determines Quality of Life, Physical Symptoms After ICU Discharge

Chiropractic Spinal Manipulation for Migraine

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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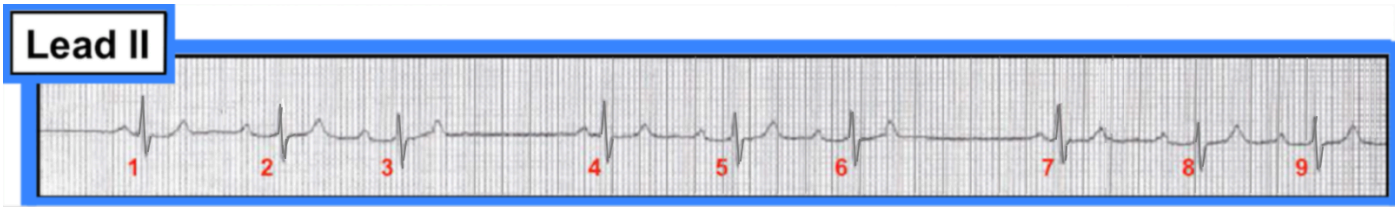
Dr. Grauer reports no financial relationships relevant to this field of study.

What Form of AV Block?

The long lead II rhythm strip shown in the figure below was obtained from a hemodynamically stable patient. The rhythm was diagnosed as showing second-degree AV block, Mobitz Type II. Do you agree with that assessment?



Our systematic approach to the interpretation of any cardiac arrhythmia is to determine hemodynamic stability first. Then, we assess for five key parameters. These essential parameters are recalled easily by the saying, "Watch your Ps, Qs, and 3Rs."

P waves. Sinus P waves are evident and recognized by the presence of upright P waves with similar morphology in this long lead II rhythm strip.

QRS width. The QRS complex is narrow. Although we would see all leads on a 12-lead ECG before committing to comment on QRS duration, the QRS complexes in this tracing clearly look to be narrow and supraventricular.

Rate. The rate of the rhythm varies, but it is neither excessively fast, nor excessively slow.

Regularity. The ventricular rhythm is not completely regular. That said, there is a pattern to this rhythm in that "group beating" is present, with three groups comprised of three beats each in a repetitive pattern.

Related. There does appear to be a consistent relation between several sinus P waves and neighboring QRS complexes. That is, the PR interval preceding beats 2/3, 5/6, and 8/9 appears to be constant, albeit slightly prolonged. Therefore, there is an underlying sinus rhythm.

What is the cause of the brief pauses between beats 3-4 and 6-7? Why is the PR interval at the end of each pause shorter than the PR interval preceding the second and third beats in each grouping? Why is the rate of sinus P waves not constant throughout this tracing?

Two clinical entities should come to mind as potential explanations for these ECG findings: some form of AV block and blocked PACs. There is no second- or third-degree AV block in this rhythm. Despite the apparent increase in PR interval between the first and second beats in each grouping, the rhythm is not AV Wenckebach. This is because the premise of AV Wenckebach (also known as the Mobitz I form of second-degree AV block) is that there should be an underlying regular sinus rhythm throughout the tracing. This is not present. The rhythm does not represent the Mobitz II form of second-degree AV block because the PR interval does not remain constant. Finally, this rhythm cannot be complete (i.e., third-degree) AV block because there is conduction of several sinus beats (i.e., beats 2/3, 5/6, and 8/9 are conducted with a constant PR interval.

The most common cause of an unexpected pause in a rhythm is a blocked PAC. This phenomenon occurs far more often than is appreciated. The reason it is so often overlooked is because of how subtle distortion of the T wave hiding the non-conducted PAC may be. Close scrutiny of the base of the T waves at the onset of each pause (i.e., the T waves of beats 3 and 6) reveals angulation that is not present in any other T wave. These blocked PACs reset the SA node and account for the pause that occurs after beats 3 and 6. Beats 1, 4, and 7 can be identified as junctional escape beats because they all manifest a slightly different QRS morphology (with taller R wave and smaller S wave) compared to the other six beats on the tracing that are sinus conducted. Further, the R-R intervals preceding beats 4 and 7 are identical, corresponding to the junctional escape rate. Finally, the reason the PR interval preceding beats 1, 4, and 7 is shorter than the PR interval preceding sinus-conducted beats is that the junctional escape focus fired before the sinus P waves preceding beats 1, 4, and 7 had a chance to conduct to the ventricles.

In summary, this is most likely a benign arrhythmia with non-conducted PACs and appropriate junctional escape beats. For further discussion on and more information about this case, please visit: http://bit.ly/2FKe3Dx.