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ABSTRACT & COMMENTARY

Trends in Supplemental Vitamin D Intake

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

SYNOPSIS: The authors investigated the trends in daily supplemental vitamin D intake of ≥ 1,000 IU and ≥ 4,000 IU and found increasing use of vitamin D supplementation.

SOURCE: Rooney MR, Harnack L, Michos ED, et al. Trends in use of high-dose vitamin D supplements exceeding 1000 or 4000 International Units daily, 1999-2014. *JAMA* 2017;317:2448-2450.

Vitamin D is a fat-soluble vitamin that either is consumed through dietary sources or synthesized when skin is exposed to ultraviolet light.[1] The benefits of adequate vitamin D intake are well demonstrated in the skeletal system, as severe vitamin D deficiency results in rickets in children and osteomalacia in adults.[1,2] The role of vitamin D in extraskeletal health is not well understood. Most evidence to support its use is from association and observational studies.[1,3,4] Some consider hypovitaminosis D, which is caused by low levels of vitamin D naturally occurring in foods and a lack of sufficient sunlight exposure, to be a pandemic worldwide.[5] Individuals with more melanin in their skin and those who use sunblock demonstrate lower rates of vitamin D synthesis resulting from sunlight exposure.[4,5] Because of inadequate dietary intake of vitamin D and decreased synthesis from sunlight exposure, many individuals require oral vitamin D supplementation.[1-8]

To assess the changes in vitamin D intake from 1999 to 2014 and investigate trends of use, Rooney et al used repeat cross-sectional data from the National Health and Nutrition Examination Survey (NHANES), which samples U.S. residents who are not institutionalized. The authors excluded participants who were pregnant, were < 20 years of age, or for whom incomplete information about supplement use was available. Participants self-reported vitamin D supplement use for 30 days. They were asked to bring supplement bottles to aid in reporting. A vitamin D supplementation level of ≥ 1,000 IU and ≥ 4,000 IU was calculated for each NHANES survey period. The researchers used Stata

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to analyze the data and calculated linear trends. A two-sided *P* value of < 0.05 was considered statistically significant. The study included 39,243 participants, with a mean age of 46.6 years (standard deviation, 16.8), 51.1% women, and 69.7% self-reported as non-Hispanic white. A significant difference was found in the prevalence of vitamin D use of 1,000 IU per day between 1999 and 2000 and 2013 and 2014. Use of vitamin D ≥ 1,000 IU in the 2013-2014 group was significantly higher at 18.2% (95% confidence interval [CI], 16.0-20.7%) compared to the 1999-2000 group, when use was 0.3% (95% CI, 0.1-0.5%; *P* for trend < 0.001). The use of ≥ 4,000 IU vitamin D prior to the 2005-2006 period was < 0.1% and was 3.2% (95% CI, 2.5-4.0%) in the 2013-2014 period.

The authors did not differentiate between vitamin D2 and vitamin D3 supplements. The increases in vitamin D supplement intake were found in most age groups, races/ethnicities, and both sexes. The use of ≥ 1,000 IU in the 2013-2014 group was highest in women (25.9%; 95% CI, 22.8-29.3%), non-Hispanic white individuals (21.8%; 95% CI, 19.3-24.6%), and those who were ≥ 70 years of age (38.5%; 95% CI, 31.8-45.7%). The use of ≥ 4,000 IU in the 2013-2014 group was highest in women (4.2%; 95% CI, 3.0-5.7%), non-Hispanic white individuals (3.9%; 95% CI, 3.0-5.1%), and individuals who were ≥ 70 years of age (6.6%; 95% CI, 4.2-10.2%).

■ COMMENTARY

Rooney et al found that U.S. adults are supplementing with increasing amounts of vitamin D, and that this increase is highest in non-Hispanic white women > 70 years of age. Three percent of the population studied exceeded the 4,000 IU tolerable upper limit, and 18% exceeded 1,000 IU per day. The recommended dietary allowance (RDA) of vitamin D is 600 IU/day for those between 1 year and 70 years of age and 800 IU/day for adults ≥ 71 years of age.[1] The American Academy of Pediatrics recommends 400 IU/day for children < 1 year of age.[6]

Over the course of the study period, there was a marked increase in the use of vitamin D supplements at the two doses documented. The authors did not discuss potential reasons or theories behind the increase in supplemental vitamin D intake. However, in 2017, the vitamin D industry was estimated to be worth $936 million.[9] Currently, serum vitamin D levels are the fifth most commonly ordered lab tests covered by Medicare.[9] Serum vitamin D tests increased 80-fold between 2000 and 2010, most likely because of growing knowledge about diseases that could be associated with low vitamin D levels.[10]

[Rooney et al found that U.S. adults are supplementing with increasing amounts of vitamin D, and that this increase is highest in non-Hispanic white women > 70 years of age.]

There are many purported uses for vitamin D; it is generally accepted that vitamin D is important physiologically. For example, the National Academy of Medicine (NAM), formerly the Institute of Medicine, concluded that vitamin D was beneficial for bone health. However, evidence is insufficient for extraskeletal health recommendations. Rather than focus on supplementation or dietary recommendations, there is some thought that vitamin D status, as determined by serum levels, is the important variable.

On this note, NAM concluded that taking a serum vitamin D (25(OH)D) level of < 12 ng/mL is indicative of possible risk for vitamin D deficiency. In addition, some people may be at risk for vitamin D deficiency at serum 25(OH)D levels between 12 ng/mL and 20 ng/mL. For most people, a serum 25(OH)D level of 20 ng/mL or higher is recommended. A 25(OH)D serum level > 50 ng/mL is associated with adverse events. Although 25(OH)D serum levels indicate exposure to vitamin D, they do not measure body storage of vitamin D and have not been shown to be a reliable marker for health outcomes.[1]

Although Rooney et al found an increasing use of supplemental vitamin D in the U.S. population, it also is possible to obtain vitamin D through diet. Few unfortified foods contain adequate amounts of vitamin D naturally. Fatty fish and fatty fish oils contain vitamin D3, and small amounts of vitamin D3 can be found in egg yolks, cheese, and beef liver.[7] Mushrooms contain vitamin D2 and may contain more amounts of vitamin D2 if exposed to light.[7] Vitamin D needs also can be met through exposure to sunlight. However, cloud cover can reduce ultraviolet energy by 50%, and ultraviolet B radiation, which is required for vitamin D3 synthesis, is unable to penetrate glass.[2]

There were several strengths in this study, including the large number of participants and the NHANES response rate of 74%. Study limitations included the lack of representation of diverse races and ethnicities, as 69.7% self-reported as non-Hispanic white, and the mean age was 46.6 years. Another major limitation was that many vitamin D supplements have been found to exceed their label claims. According to Labdoor, a company that tests supplements, an analysis of 19 of the best-selling vitamin D supplements in the United States found that all the products tested exceeded their vitamin D label claims by 22%, and six products exceeded their label claims by 40%.[11] Multivitamins usually contain label claims of 400 IU/day. Vitamin D intakes > 1,000 IU per day may indicate additional supplemental vitamin D intake. Furthermore, no distinction was made between different formulations of vitamin D (i.e., vitamin D2 vs. vitamin D3). There may be variable physiological effects between these supplements.[5]

Since some participants' vitamin D intakes exceeded the RDA, there might be concerns about vitamin D toxicity. Gailor et al reviewed case reports of vitamin D toxicity, which included information about how much vitamin D was taken, the serum vitamin D level at the time of admission, and a complete medical evaluation.[10] They found that most cases of vitamin D toxicity are due to intake of vitamin D supplements that exceed their label claims.[10] The authors found that serum levels > 150 ng/mL posed toxicity risks and should be avoided.[10] Vitamin D intoxication leads to hypercalcemia through higher calcium absorption in the gut and hypercalciuria. Rising calcium levels also may lead to muscle weakness, hypertension, neuropsychiatric symptoms, renal toxicity, and renal calculi.10 Of note, the official upper level is 4,000 IU in adults and children ≥ 9 years of age.

Although reports of vitamin D toxicity appear to be rare, the growth in vitamin D supplement use may increase adverse events. Unfortunately, supplemental vitamin D label claims do not always reflect the actual concentration in the supplement, making it difficult to recommend vitamin D supplements. Certain populations are at risk of vitamin D deficiency, including breastfed infants, people with limited sun exposure, people with dark skin, older adults, people with lower fat absorption, individuals with inflammatory bowel disease, people with obesity, and those who have undergone gastric bypass surgery.[1,2,3,6,8] Although serum 25(OH)D levels are the best indicator of vitamin D status, they are not indicative of storage levels of vitamin D in tissue.[4,5,7] Patients take vitamin D supplements, so it is important for providers to obtain accurate lists of any other supplements they take. In patients at risk for vitamin D deficiency, obtaining a serum 25(OH) D level may be helpful when recommending adequate amounts of vitamin D through diet, sun exposure, and multivitamin or supplement use. Providers should monitor serum 25(OH)D levels during treatment to ensure that supplementation is not excessive. In all patients, especially those at risk for adverse events due to high intake of vitamin D supplements, education about the inaccuracy of label claims of many vitamin D supplements and risks of toxicity is important. ■

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ABSTRACT & COMMENTARY

Is Sanitizer Better Than Soap?

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: In day care settings, the implementation of hand hygiene programs reduced respiratory illness, absenteeism, and antibiotic use in children 0-3 years of age. Using hand sanitizer was more effective than washing with soap and water.

SOURCE: Azor-Martinez E, Yui-Hifume R, Muñoz-Vico FJ, et al. Effectiveness of a hand hygiene program at child care centers: A cluster randomized trial. *Pediatrics* 2018;142:e20181245.

Respiratory tract infections are a major cause of illness, medical office visits, and antibiotic prescriptions for preschool-age children. Attendance at day care centers is a significant risk factor for becoming ill with respiratory tract infections, and children in day care contract six to 10 respiratory tract infections each year. In school-age children, implementation of hand hygiene interventions reduces infections and school absenteeism. However, there are not many data about the effectiveness of hand hygiene programs in preschoolers in day care settings.

Azor-Martinez et al randomized day care centers (and the attending children) to either hand hygiene (with groups randomized to use soap and water or hand sanitizer) or control groups. The authors found 25 state-registered day care centers in the area of a single city in Spain. Researchers included families of children 0-3 years of age who attended day care for at least 15 hours per week. Children with chronic illnesses and medication use that might alter the risk of respiratory tract infection were excluded.

Prior to the study period, parents and day care center staff who were randomized to an intervention group attended a one-hour workshop about hand hygiene. Participants were encouraged not to alter their usual post-toileting cleaning or the manner by which they cleaned visibly dirty hands. However, they were instructed to use the intervention (soap-and-water washing or sanitizer use) before and after lunch, after outdoor play, prior to leaving school for home, after diapering, and after sneezing, coughing, or blowing their noses.

Sanitizer (70% alcohol) or soap (not specifically bactericidal) was provided for the schools and homes. Informational brochures about hand hygiene were available in the intervention day care centers. All day care centers, both in the intervention and control groups, provided informational sessions about respiratory infections and fever. Children were followed carefully for eight months.

The study included 960 children (82% of those who were eligible; the others did not secure parental authorization for participation) from the 25 day care centers. One child in the sanitizer group exhibited worsened atopic dermatitis; no other adverse effects were noted. More than three-fourths of children received a 13-valent pneumococcal vaccine. Receipt of this bacterial vaccine did not significantly alter the risk of contracting a respiratory illness.

Overall, the 960 children contracted 5,211 respiratory illnesses during the eight-month study period. Children received antibiotics for 39% of those illnesses. The rate of respiratory infection was 21% lower in the sanitizer group than in the soap-and-water group, and 23% lower than in the control group. Day care absenteeism was significantly lower in the intervention groups (3.3% with sanitizer, 3.9% with soap and water) than in the control group (4.2%).

The rate of antibiotic use was 31% lower in the sanitizer group than in the control group (which was similar to the soap-and-water group in terms of antibiotic use). The authors concluded that hand hygiene education and practice (whether with sanitizer or soap and water) reduced day care center absenteeism. Interestingly, children assigned to use sanitizer contracted significantly fewer infections, were not absent from day care as often, and took fewer antibiotics than those who used soap and water for hand hygiene.

■ COMMENTARY

What seems right is right — hand hygiene is effective in reducing illness and missed activity in preschool-age children. This is congruent with experience in older school-age children, but the availability of hand hygiene materials must be supplemented by instruction that promotes helpful behaviors.[1]

Even though the impact of hand hygiene programs varies between settings,[2] many medical and education professionals are aware of the value of hand hygiene.

Many child care settings have implemented hand hygiene protocols.

As we think back over the past two decades, we realize that hand hygiene in hospitals became a standard not just because of knowledge about the value of hand hygiene. Rather, people started cleaning their hands upon entering and exiting hospital rooms when hand hygiene became easy and convenient. The results of a systematic review suggested that multimodal tactics are needed to improve compliance with hand hygiene most effectively.[3,4] Similarly, hand hygiene should become easy and convenient in day care centers and schools.

Why was sanitizing more effective than hand washing in this study? There are several potential explanations. First, sanitizer kills germs while soap and water "just" removes germs from hands. Future studies could compare the use of regular and bactericidal soaps in preventing infection in day care settings. Second, the authors did not measure compliance with the implementation of sanitizing programs. It could be that hand washing was implemented less in the day care centers assigned to that intervention because it was not as easy or convenient. Hand washing requires sinks, a means of drying, and a longer pause at the sink. Sanitizing simply requires a quick hand motion across an air dispenser and some hand rubbing while moving on to the next activity. Whatever means of hand hygiene is suggested, success depends on effective implementation. Third, the authors did not mention the means of drying in the soap and water group. Hand washing is most effective in reducing bacterial colonization when accompanied by the use of a sterile (rather than non-sterile) towel.[5] If wet towels were reused repeatedly, the towels might have served as reservoirs of infection to facilitate ongoing microbial transmission.

Sanitizer use in hospitals might be facilitated by programs that ask patients to remind care providers to use sanitizer before and after patient contact.[6] Similarly, parents and even children can be empowered to ensure that sanitizer is available conveniently in day care settings and for individual student use. By whatever means, hand hygiene can prevent illness in preschool-age children, decrease absence from planned activities, and reduce costs of medical care. It is time for implementation. ■

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PHARMACOLOGY UPDATE

Sarecycline Tablets (Seysara)

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 narrow-spectrum tetracycline-class antibiotic for the treatment of moderate to severe acne vulgaris. Sarecycline is distributed as Seysara.

INDICATIONS

Sarecycline is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne in patients 9 years of age and older.[1]

DOSAGE

The recommended dosage is based on body weight.[1] For patients who weigh 33-54 kg, the dosage is 60 mg once daily. For patients who weigh 55-84 kg, the dosage is 100 mg once daily. For patients who weigh 85-136 kg, the dosage is 150 mg once daily.

Sarecycline is available as 60 mg, 100 mg, and 150 mg tablets.

POTENTIAL ADVANTAGES

Sarecycline is active against gram-positive cocci but is 16- to 32-fold less active than the commonly used minocycline and doxycycline against gram-negative bacilli.[2] Sarecycline also is less active than other tetracyclines against gram-positive and gram-negative anaerobic organisms. Potentially, this means there is a lower effect on the normal intestinal microbiome, which may reduce the risk of the emergence of tetracycline-resistant organisms (including overgrowth of *Candida albicans*).[2] The drug is dosed once a day, potentially improving compliance.

POTENTIAL DISADVANTAGES

The efficacy and safety beyond 12 weeks have not been established.[1] The most frequently reported adverse reaction was nausea (4.6% vs. 2.6% for placebo).[1] Sarecycline shares the same warnings as the tetracycline class (e.g., teratogenic effects, intracranial hypertension, photosensitivity).[1]

COMMENTS

The efficacy and safety of sarecycline was evaluated in two, 12-week, randomized, double-blind, placebo-controlled trials that included 2,002 subjects.[1,3,4] Subjects had moderate to severe facial acne and scored ≥ 3 on the Investigator Global Assessment (IGA) scale. IGA is a five-point scale assessing acne severity as clear, almost clear, mild, moderate, and severe. In addition, subjects had 20-50 inflammatory lesions and ≤ 100 noninflammatory lesions, and ≤ 2 nodules. These subjects were randomized to sarecycline 1.5 mg/kg/day or placebo. There were two coprimary endpoints: percentage of subjects' IGA success (defined as a score of clear [0] or almost clear [1]) and absolute reduction from baseline in inflammatory lesion counts.

IGA success rates vs. placebo were 21.9% vs. 10.5% in trial 1 and 22.6% vs. 15.3% in trial 2. Mean absolute reductions in inflammatory lesions were 15.3 vs. 10.2 in trial 1 and 15.5 vs. 11.1 in trial 2. Mean percent reductions were 52.2% vs. 35.2% in trial 1 and 50.8% vs. 36.4% in trial 2. Researchers observed a reduction in inflammatory lesions by the first visit (week 3) and in noninflammatory lesions between weeks 6 and 9. The authors of an open-label extension study did not observe any significant safety issues among participants receiving sarecycline for up to 40 weeks.[3,6] Participants in this extension study were treated until adequate improvement in facial acne was achieved. Treatment restarted if acne recurred.

CLINICAL IMPLICATIONS

Acne is a common inflammatory disorder most often affecting adolescents but also adults.[5] Systemic antibiotics are recommended for moderate and severe acne and forms of inflammatory acne that are resistant to topical treatment.[5] Doxycycline and minocycline are used commonly. Sarecycline is the first narrow-spectrum tetracycline-class antibiotic developed for acne by targeting *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) as well as other important skin/soft tissue pathogens with little or no activity against enteric gram-negative bacilli. It is unknown whether this potential advantage will translate into measurable clinical benefit. The cost for sarecycline is $1,032 for a 30-day supply. ■

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CME QUESTIONS

1. **Which of the following statements regarding vitamin D supplementation is *false*?**
   a. Vitamin D supplements have been found to contain higher amounts of vitamin D than the label claims.
   b. Vitamin D use in the United States has decreased since 1999.
   c. Serum 25(OH)D levels at ≥ 150 ng/mL are associated with toxicity.
   d. Serum 25(OH)D levels are not indicative of body storage of vitamin D.

2. **Which of the following is true of the use of hand sanitizer in day care settings?**
   a. The rate of respiratory illness declined.
   b. Absenteeism rates were not affected.
   c. Those in the hand sanitizer group took more antibiotics.
   d. Soap and water was more effective than hand sanitizer.

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]

Clinical Outcomes After Oral Anticoagulant-Associated Intracerebral Hematoma

PCSK9 Inhibitors in Acute Coronary Syndrome Patients

Hormone Therapy and Mortality: No Overall Effect?

Internal Medicine [ALERT]

ECG Review

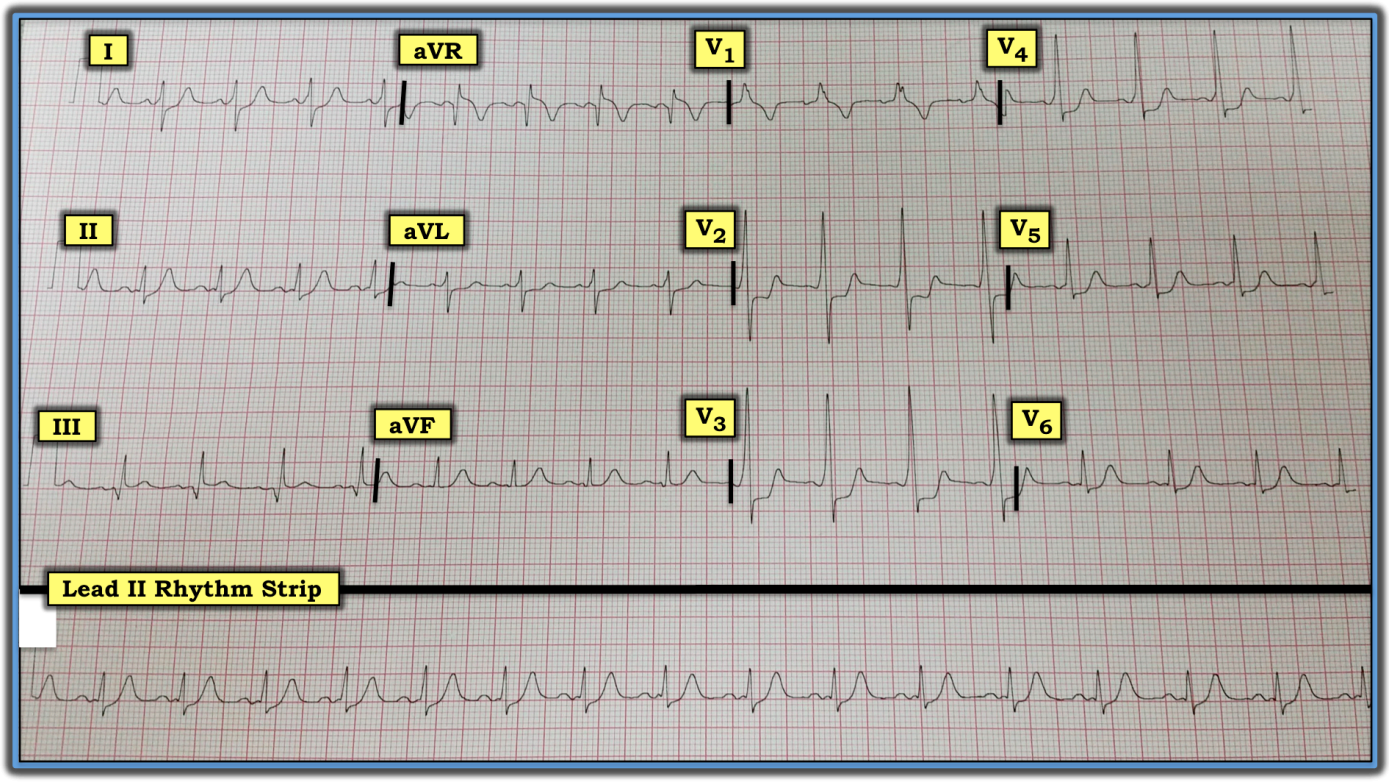
By Ken Grauer, MD

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

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

Is There RBBB, Acute Ischemia, or Both?

The ECG in the figure was obtained from a 35-year-old man with a 20-year history of smoking. He presented to the ED with new-onset chest discomfort. He was hemodynamically stable at the time this tracing was obtained. How would one interpret his ECG? Is there right bundle branch block (RBBB)? Is there evidence of acute posterior ischemia or infarction?



There is a regular sinus rhythm at ~90 beats/minute. At first glance, the PR interval looks normal and the QRS looks wide with a pattern in lead V1 that suggests RBBB. That said, this is not RBBB. Delta waves with a short PR interval are visible in several leads, most notably in leads V2, V3, and V4. Instead of RBBB, this patient has Wolff-Parkinson-White (WPW) syndrome.

Once one realizes this patient has WPW, it becomes clear that the negative initial deflection in lead III is not a Q wave but rather a negative delta wave. Other examples of "retrospective recognition" of delta waves on this tracing are visible in leads II, aVL, and aVF. Thus, the suggestion of a tiny "extra little bump" on the baseline in leads II and aVF probably represents subtle delta waves that are almost entirely isoelectric.

The other remarkable finding on this tracing is the marked ST segment depression in leads V2-V5. Most of the time, one cannot appreciate ischemia or acute infarction in a patient with WPW. That said, on occasion ST-T wave changes may be so marked as to suggest acute disease, necessitating cardiac catheterization to define the anatomy. This was the situation in this case. Suffice it to say that the cardiologist also was uncertain as to whether the ST segment depression in multiple chest leads was a marker of acute ischemia or simply an accompaniment of this patient's WPW. As a result, prompt cardiac catheterization was performed. It turned out that the coronary arteries were free of significant disease.

For more information about and further discussion on this case, please visit: https://bit.ly/2FR4LbS.