Letters to the Editor

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Interpreting and Evaluating the Details of the JUPITER Study

Original Article: The JUPITER Study: Biomarkers Plus Statin vs. Lifestyle Modification for Preventing Cardiovascular Events [Editorial]

Issue Date: March 15, 2009

Available at: http://www.aafp.org/afp/2009/0315/p438.html

TO THE EDITOR: I would like to question some of the assumptions and conclusions of the editorial on the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) study. The authors start with an unproven assumption: a study of 1,315 community sites cannot have high-level quality control. As the chief investigator at one of the study sites, I can assure you that the monitoring and control were thorough, careful, and vigorous. The importance of community-based studies should not be belittled—they come much closer to an interface with real practice conditions than research institution sites. The long list of exclusion criteria is necessary to assure safety and a valid study effect. If anything, the community-based studies are biased toward the less-ill patients, which would minimize the study effect.

It is misleading to consider death as the only relevant endpoint when the study also used cerebrovascular and cardiovascular events as endpoints, both of which are important. It is also misleading to criticize the tight exclusionary data as a weakness. These data made recruitment for the study difficult, but minimized the potential impact of confounding variables. The issue is not one of comparing lifestyle management with a medication, but to see if there is a clinical benefit from treating inflammation as a cardiac risk factor independent of other interventions.

Physicians are tasked with preventing cardiovascular disease when possible. There are multiple risk detection tools available: family history, smoking, diet, lack of exercise, hypertension, and lipid levels. I believe we can now add inflammation to this list. Similarly, we can possibly add to our armamentarium of lifestyle interventions, blood pressure reduction, and lipid reduction, which can affect inflammation reduction. We have a responsibility to select and use all available tools.

The arguments about numbers needed to treat are fraught with misleading assumptions. JUPITER data do not argue for screening patients who meet the study exclusion criteria, or the general population. The data do not argue for considering C-reactive protein measurements in patients with a normal lipid profile, but who are otherwise at risk of cardiovascular disease. The study authors calculated that the number of patients who would need to be treated with rosuvastatin (Crestor) for four years to prevent one adverse event would be 31.[1]

The findings of the JUPITER trial were dramatic. The study was terminated after an average of 1.9 years of follow-up because of marked divergence between the treatment and placebo groups. Such early termination of a study powered to detect endpoints such as cardiovascular events or death in favor of treatment is nearly unprecedented. The *P* value arguing in favor of a meaningful difference was .000001.[1] A wise physician would not ignore such dramatic findings.

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Author disclosure: Dr. Neft was a principal investigator in the JUPITER study, which was sponsored by Astra Zeneca.

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IN REPLY: Dr. Neft disagrees with several elements of our editorial. First, he claims we ▶

stated that a study with 1,315 community sites cannot have high-level quality control. Actually, we said it is more difficult to achieve quality control when only a handful of patients are enrolled per site. The average site enrolled 13 patients over 3.5 years, or about one patient every three months.

He then argues that the community setting improves relevance and more closely resembles the real world, but then states that a long list of exclusion criteria are necessary to assure safety and a valid study effect. But, study participants either look like the typical patient or they are highly selected to have the best chance of responding to the treatment in question—not both. He argues that the extensive exclusion criteria are necessary to "minimize the potential impact of confounding variables." However, if done properly, randomization takes care of that by assuring that known and unknown confounding variables are evenly distributed between treatment and control groups.

Dr. Neft states that we ignore the benefit of fewer strokes (0.18 versus 0.34 per 100 person years) and fewer myocardial infarctions (0.17 versus 0.37 per 100 person years). The corresponding numbers needed to treat (NNT) for the two-year study period were approximately 300 and 250 for these conditions, respectively. Remember, these small benefits were seen in a fairly high-risk group of patients. Despite their normal low-density lipoprotein (LDL) cholesterol, their average age was 66 years; 40 percent had metabolic syndrome; most were hypertensive; one in six smoked; only one in six took aspirin; and one half had at least a 10 percent 10-year risk of heart disease. These modest benefits, achieved at a very high cost, will be much less impressive when applied to typical primary care patients and younger patients who are at lower risk.

The JUPITER trial's primary endpoint included "all bad things" (a much criticized practice)[1] and had an NNT of 85. Approximately eight patients must be screened to identify one with the combination of normal LDL and elevated C-reactive protein studied in the JUPITER trial. Dr. Neft says the JUPITER trial does not argue for screening, but how else are we to apply the results in practice?

The size of the *P* value is a reflection of the enormous size of the study, not the magnitude of the effect. With almost 18,000 patients, even a small and clinically unimportant difference can generate an "impressive" *P* value. It is important to look at the NNT or harm, not just the *P* values.

We stand by our primary assertions: the benefit demonstrated by the JUPITER trial is modest and comes at a very high cost, and non-drug approaches have been shown to have more important benefits at a lower cost. This trial is a good example of what happens when the drug industry studies questions of interest to them, rather than when physicians and scientists study questions of importance to patients. For example, comparisons of rosuvastatin (Crestor) with less expensive generic statins, with low dose aspirin, and with diet and exercise would provide valuable information for our practices. Unfortunately, we are unlikely to see those comparisons in an industry-sponsored clinical trial.

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Vitamin D Supplementation in Patients with Tuberculosis

Original Article: Recognition and Management of Vitamin D Deficiency

Issue Date: October 15, 2009

Available at: http://www.aafp.org/afp/2009/1015/p841.html

TO THE EDITOR: Dr. Bordelon and colleagues provide a timely and useful summary of the management of vitamin D deficiency. However, they cite tuberculosis as a contraindication to vitamin D supplementation, which is not the case. Activated macrophages produce elevated amounts of 1-α-hydroxylase, which can potentially produce toxic levels of 1,25-dihydroxyvitamin D if adequate substrate 25-hydroxyvitamin D is available; therefore, there are concerns about the risk of hypercalcemia in patients with tuberculosis or other granulomatous diseases.

In 1984, Narang and colleagues reported high rates of hypercalcemia in patients with or without tuberculosis receiving vitamin D supplementation,[1] forming the basis of these concerns. However, these results have not been reproduced and are speculated to have stemmed from underestimating the actual amount of vitamin D administered in the study.[2]

More recent data show that vitamin D supplementation in patients with tuberculosis does not appear to be ▶

associated with hypercalcemia. In preliminary safety data from one study, 11 patients with tuberculosis were administered a single dose of 100,000 IU ergocalciferol (vitamin D_2).[3] At eight weeks, there was a significant rise in serum vitamin D_2 levels and no episodes of hypercalcemia. In a randomized trial of 100,000 IU cholecalciferol (vitamin D_3) in patients with tuberculosis in Guinea-Bissau,[4] there was no difference in hypercalcemia symptoms or detection of biochemical hypercalcemia in those randomized to the treatment arm; however, patients in the treatment arm did not attain higher serum vitamin D levels than those randomized to placebo, suggesting that the vitamin D formulation used (an injectable preparation given orally) may have been poorly absorbed. Other studies, summarized elsewhere,[5,6] have also reported safe administration of vitamin D in patients with tuberculosis.

Given the evidence of the potential benefits of vitamin D_3 in the immune response to *Mycobacterium tuberculosis*,[6] optimizing vitamin D levels (while monitoring calcium levels) should not be considered contraindicated in patients with tuberculosis. Results from trials of vitamin D adjunctive therapy that are currently underway will provide further clarification of the benefit, if any, of vitamin D supplementation in patients with tuberculosis.

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EDITOR'S NOTE: This letter was sent to the authors of "Recognition and Management of Vitamin D Deficiency," who declined to reply.

Malaria Chemoprophylaxis and Travel Immunizations

Original Article: The Pretravel Consultation

Issue Date: September 15, 2009

Available at: http://www.aafp.org/afp/2009/0915/p583.html

TO THE EDITOR: The article on pretravel consultation by Drs. Bazemore and Huntington presents a broad overview of the role of family physicians in preparing patients for safe travel. However, the article contains some important errors and omissions.

Regarding malaria chemoprophylaxis, the article indicates that atovaquone/proguanil (Malarone) is not recommended for children weighing less than 24 lb (11 kg). The Centers for Disease Control and Prevention (CDC) has advised that this drug is safe to use in children weighing as little as 11 lb (5 kg) in a dosage of one half of a pediatric pill per day.[1] The pill may be crushed and mixed with formula or food.

Although chloroquine (Aralen) is rapidly absorbed, its extensive sequestration in body organs necessitates more than a single dose to achieve therapeutic levels. The drug should be started one to two weeks—not one to two days—before exposure to chloroquine-sensitive malaria. This also provides a window of time before traveling to assess how well the drug is tolerated. Similarly, mefloquine (formerly Lariam) requires multiple doses to achieve therapeutic levels. Relative resistance to mefloquine is not unusual, and subtherapeutic drug levels are not only potentially ineffective, but may add to selective pressure for resistance. Some physicians advocate a loading dose of 250 mg per day for three days, followed by 250 mg per week during exposure and for one month after exposure. No matter how the loading dose is administered, one tablet one to two days before exposure is not sufficient.[2]

The information presented on doxycycline is correct, but an important consideration is that patients may travel to areas endemic for leptospirosis and rickettsial infections. Both of these infections are effectively prevented with doxycycline.

The authors describe the mouse brain–derived Japanese encephalitis vaccine (Je-vax), which is no longer being produced and has limited availability. It is available only for pediatric use. Ixiaro is a new Japanese encephalitis vaccine that appears to have fewer adverse effects. It is approved for use in patients 17 years and older, and is given as two doses spaced 28 days apart.[3]

According to the CDC, a booster dose of the meningococcal polysaccharide vaccine (Menomune) should be

given every five years if the patient received the first dose after 10 years of age. It is licensed for use in patients two years and older. However, Menomune has been largely supplanted by the meningococcal conjugated vaccine (Menactra) because of its longer duration of protection. Menactra is licensed for use in patients two to 55 years of age. Menomune is the preferred form in pregnant women who are at risk of meningitis.[4]

The tuberculosis (bacillus Calmette-Guérin) vaccine is rarely given in the United States, but it may be appropriate in young children traveling to high-risk locations. It is often required for school entry in other parts of the world. When it is used in the United States, it is given via a multipuncture device, not intradermally.[5]

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IN REPLY: We appreciate Dr. Jones' interest and helpful comments. The pediatric dosing limitation for atovaquone/proguanil (Malarone) cited in our article references the approved package insert at the time the manuscript was submitted. Although the Centers for Disease Control and Prevention (CDC) recommends using this drug in children weighing less than 24 lb (11 kg), this use is currently off-label. We also appreciate Dr. Jones' pointing out a typographical error in the recommended initiation point for prophylactic chloroquine (Aralen) and mefloquine (formerly Lariam) use, which is indeed one to two weeks—not days—in advance of travel.

We also agree that Ixiaro, which was not yet approved at the time of our manuscript's publication, is now the preferred pretravel vaccination for Japanese encephalitis. We appreciate the details provided by Dr. Jones on meningococcal conjugate and bacillus Calmette-Guérin (BCG) vaccines, a full discussion of which was not possible because of space limitations. The footnotes in Table 4 of our article regarding both of these drugs came from the manufacturer's package inserts. Reports by the Canada Communicable Disease Report and the Morbidity and Mortality Weekly Report (MMWR) note that the BCG vaccine may be rendered intradermally or subcutaneously.[1,2] The MMWR states, "BCG vaccinations are usually administered by the intradermal method, and reactions…can be expected after vaccination. …Higher rates of local reactions may result from using subcutaneous injection in comparison with reactions from intradermal injection."[2] Travel practitioners rendering evidence-based advice will discover occasional disagreement among recommendations from the CDC, drug manufacturers, proprietary decision-support tools, and practices in other developed nations.

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