Correspondence

Prevention of Venous Thromboembolism with Fondaparinux

To the Editor: Eriksson et al. (Nov. 1 issue)[1] report that fondaparinux was more effective than enoxaparin and equally safe in preventing venous thromboembolism after hip-fracture surgery. In their study, the first dose of enoxaparin was to be administered 12±2 hours preoperatively and the second dose 12 to 24 hours postoperatively, according to the recommendation of the manufacturer. However, enoxaparin was first given postoperatively in as many as 74.4 percent of the patients in the enoxaparin group. The delay in the initiation of enoxaparin may have resulted in an underestimation of its preventive effects against thromboembolism and its hemorrhagic risks, thus obscuring the relative effects of fondaparinux. Since significant unrecognized bias may exist, the results must be interpreted with caution. A better explanation of why the treatment of the majority of the patients did not conform to the study protocol would be beneficial for readers.

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1. Eriksson BI, Bauer KA, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001;345:1298-304.

To the Editor: Several methodologic issues have to be considered in interpreting the results reported by Eriksson et al. Other investigators have found that the initiation of antithrombotic prophylaxis close to the time of surgery is more effective than delaying prophylaxis and that the efficacy of fondaparinux is dose-dependent.[1-4] It is therefore apparent that the superiority of the pentasaccharide reported by Eriksson et al. reflects the timing of the initiation of treatment in the early postoperative period, the doubling of the dose within 24 hours after surgery, and the administration of one additional dose during the study period.

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To the Editor: In his editorial, Diuguid[1] suggests that low-molecular-weight heparins need to be administered preoperatively to provide maximal benefit. The timing of the commencement of treatment with heparin and low-molecular-weight heparins has been long debated; a recent study suggests that there is no difference in efficacy.[2] This absence of a difference weakens the editorialist's suggestion that fondaparinux "may find its initial niche in patients undergoing regional anesthesia" because of the fact that it can be commenced postoperatively. The pharmacologic profile of fondaparinux does not make it more suitable than other agents to use in combination with regional anesthesia. On the contrary, it is long acting and its effects are difficult to

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monitor or reverse, so that the precautions required when spinal or epidural anesthesia is combined with perioperative fondaparinux would need to be as stringent as those for low-molecular-weight heparins, if not more so. At present, there appears to be no reason to commence fondaparinux therapy any earlier or later after surgery than treatment with any of the low-molecular-weight heparins is begun, and in my opinion, a fair comparison of the efficacy of these agents has not yet been performed.

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To the Editor: After reading Dr. Diuguid's editorial, I still have a question concerning the choice of low-molecular-weight heparins for the treatment of venous thromboembolism. Is it permissible to recommend dalteparin instead of enoxaparin for the treatment of venous thromboembolism, especially if there are major differences in cost? Are we taking a leap of faith to use these low-molecular-weight heparins interchangeably, or should this be the standard of care?

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Dr. Eriksson replies:

To the Editor: Drs. Murashige and Kami and Dr. Marlovits comment on the timing of the first doses of enoxaparin and fondaparinux in our study. According to the study protocol, the first dose of enoxaparin was to be given 12±2 hours preoperatively, except that omission of the preoperative injection was recommended if the use of regional anesthesia or epidural catheterization was planned. This approach is in line with the recommendations of health authorities in Europe. Because in many cases, surgery was performed soon after admission and the use of regional anesthesia was planned, only 25.6 percent of patients received this injection. This outcome reflects the usual situation in clinical practice, in which it is difficult to administer antithrombotic agents preoperatively in emergency situations. My colleagues and I think that this practice did not result in an underestimation of the prophylactic effect of enoxaparin. Furthermore, in one study, treatment with enoxaparin (40 mg) was initiated preoperatively in 78.1 percent of patients who were undergoing elective hip surgery, and this approach was significantly less effective in preventing deep-vein thrombosis than was the postoperative initiation of fondaparinux.[1]

The regimen of fondaparinux was selected from a large, phase 2 trial.[2] A post hoc logistic-regression analysis of all phase 3 studies involving patients who first received fondaparinux between three and nine hours after orthopedic surgery showed that there was no significant relation between the timing of the first injection and efficacy.[3] The hypothesis that administering low-molecular-weight heparins close to the time of surgery may increase efficacy has not been tested in a direct comparison.

Dr. Marlovits suggests that the superior efficacy of fondaparinux may reflect a disparity between the number of fondaparinux and enoxaparin injections. This is unlikely because a median of 7 injections of fondaparinux (range, 1 to 11) and of enoxaparin (range, 2 to 10) were administered up to the time of the qualifying examination for venous thromboembolism. Furthermore, in a companion study of patients undergoing elective knee surgery,[4] 30 mg of enoxaparin administered twice daily was significantly less effective in preventing deep-vein thrombosis than was fondaparinux administered in the same dose regimen that we used.

We believe that factors other than the timing of the initial dose contributed to the superior efficacy of fondaparinux, such as the ability of this agent to inhibit activated factor X selectively and the rapid onset of action and optimal half-life of this agent.

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The editorialist replies:

To the Editor: Priestley cites a study by Hull et al. to bolster his argument that there is no difference between preoperative and postoperative administration of dalteparin in terms of the prevention of venous thromboembolism after hip surgery. However, Hull et al.[1] reported an incidence of venous thromboembolism of 19.7 percent, which was virtually identical to the rate of 19.1 percent reported by Eriksson et al. in the enoxaparin group in their trial and considerably higher than the incidence of 8.3 percent reported in the fondaparinux group.[2] Several earlier studies of preoperatively administered low-molecular-weight heparins have reported rates of venous thromboembolism similar to that associated with fondaparinux therapy, but the preoperative administration of these drugs is contraindicated in patients who receive regional anesthesia.

I share Priestley's concern about the pharmacologic

profile of fondaparinux, especially since the problems with low-molecular-weight heparins became apparent only after the drugs had been on the market for several years. I agree that the precautions for the use of fondaparinux should be similar to those for the use of low-molecular-weight heparins. However, I think that the current data support strong consideration of the use of fondaparinux as prophylaxis against venous thromboembolism in high-risk patients, especially those who receive regional anesthesia, since such patients cannot receive low-molecular-weight heparins preoperatively.

Scacewater raises a legitimate question about the interchangeability of low-molecular-weight heparins in the treatment of venous thromboembolism. These drugs have clear differences in their pharmacologic profiles. It is not clear, however, that these differences result in clinically significant differences in efficacy. All the studies conducted to date have compared low-molecular-weight heparin with unfractionated heparin, and they have shown that dalteparin, enoxaparin, and tinzaparin, given in appropriate anticoagulant doses, are equivalent to unfractionated heparin in terms of both safety and efficacy. Although a head-to-head trial of the low-molecular-weight heparins would be ideal, from the data available it follows that these agents are equivalent in the treatment of venous thromboembolism and that the choice can be based on the preference of the physician, patient, or institution.

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Estrogen-Replacement Therapy after Ischemic Stroke

To the Editor: Viscoli et al. (Oct. 25 issue)[1] report that estrogen-replacement therapy does not reduce the risk of stroke in women with a history of cerebrovascular disease. The fact that the women in this study were treated with estrogen alone, without a progestin ("unopposed estrogen"), arouses concern. The mitogenic effect of unopposed estrogen on the endometrium has been an issue of concern for decades.[2] In 1995, a randomized clinical trial, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, verified the hazards of the use of unopposed estrogen with respect to endometrial hyperplasia and hysterectomy.[3] On the basis of these and other emerging data, in 1994 the Women's Health Initiative (in which two of us are coinvestigators) stopped randomly assigning women with an intact uterus to receive estrogen alone and subsequently randomly assigned only women who had undergone a hysterectomy to that intervention.

In the study by Viscoli et al., the use of annual endometrial biopsies to screen the endometrium may have minimized the harm caused by giving unopposed estrogen[3]; early cancers may have been detected through surveillance. But this strategy is clearly suboptimal, since it entails the promotion of abnormal endometrial growth on the basis of the rationale that any resulting cancers will be surgically removed.

Given the results of the PEPI trial and the change in protocol by the Women's Health Initiative (from 1995 to 1998), we wonder how Viscoli et al. weighed the known risks of unopposed estrogen against the unknown benefits of secondary stroke prevention. Their continued use of unopposed estrogen is particularly puzzling because they could have adopted the strategy of the Women's Health Initiative and confined the use of unopposed estrogen to women who had had a hysterectomy.

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The authors reply:

To the Editor: The goal of our study was to test the effectiveness of estrogen for the prevention of death and recurrent stroke in women with cerebrovascular disease. Several lines of evidence supported the study of unopposed estrogen in this setting. First, the extensive epidemiologic evidence in support of the vascular protective effects of estrogen involves almost exclusively studies in which estrogen was used alone (without progestin therapy).[1] Second, progestins antagonize many of the vascular protective mechanisms of estrogen.[2,3] Therefore, we designed the study to identify the hormonal regimen with the greatest likelihood of protecting women against recurrent cerebrovascular disease. Given the negative results of the study, if we had tested combined estrogen–progestin therapy, we would have been unable to determine whether the negative results were due to the ineffectiveness of estrogen or to the adverse effect of the progestogen. Indeed, one of the proposed explanations for the results of the Heart and Estrogen/Progestin Replacement Study is that the increased early risk of cardiovascular events may have been caused by the medroxyprogesterone acetate, not the estrogen.[4]

It was also unclear whether the effects of estrogen on the endometrium in the PEPI trial could be generalized to women in our study, whose average age was 71 years (as

compared with an average age of 56 years in the PEPI trial).[5] Because the uterus is typically atrophic in elderly women, it was uncertain whether estrogen therapy alone would be associated with similar risks in this population.

To ensure the participants' safety, all women with a uterus were prescribed medroxyprogesterone once a year, so that we could detect early hyperplastic changes in the endometrium that could be treated effectively; were evaluated thoroughly for any episode of unscheduled bleeding; and underwent ultrasonography or endometrial biopsy at the end of their participation in the study. The average duration of estrogen exposure in the trial was three years — an interval we consider to be relatively short. Only two cases of uterine cancer were detected, both within six months after randomization, suggesting that estrogen-replacement therapy unmasked preexisting cancers. No other cases of endometrial cancer occurred during the follow-up period.

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Recognition and Management of Anthrax

To the Editor: In his timely review of anthrax, Swartz (Nov. 29 issue)[1] states that "incision or débridement of such early [cutaneous] lesions should be avoided, since this may increase the possibility of bacteremia." We believe that this prohibition does not apply to diagnostic skin biopsies.

Eight of 12 patients in whom cutaneous anthrax has been diagnosed since early October have undergone biopsies of their skin lesions. Immunohistochemical staining for the capsule and cell-wall antigen of *Bacillus anthracis* was positive in each case and provided essential diagnostic information.[2-5] All other serologic studies or skin tests were less sensitive. For example, in the initial patient with cutaneous anthrax, culture and Gram's staining of serous fluid from skin lesions were negative, but immunohistochemical analysis of the skin established the diagnosis.[3] If a patient has already started receiving appropriate antibiotics, attempts to culture *B. anthracis* will be thwarted, but an immunohistochemical analysis of the skin will remain positive.

When we were preparing an algorithm for evaluating patients with suspected cutaneous anthrax for the Bioterrorism Taskforce of the American Academy of Dermatology (available at http://www.eblue.org/anthrax), we tried to trace the origin of the oft-repeated caution regarding surgical manipulation. We were unable to find a primary reference or further substantiation. The remark may predate the antibiotic era. Without antibiotics, bacteremia might change the course of (usually benign) cutaneous disease into (usually lethal) systemic disease. Today, with the simultaneous administration of antibiotics, the danger is minimal. Our algorithm, which is consistent with the one published by the Centers for Disease Control and Prevention,[4] recommends the biopsy of suspicious lesions.

(The opinions expressed in this letter are those of the authors and are not necessarily those of the Department of Defense.)

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1. Swartz MN. Recognition and management of anthrax — an update. N Engl J Med 2001;345:1621-6.
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To the Editor: Dr. Swartz recommends the use of contact precautions for patients with draining cutaneous lesions and standard precautions for all others hospitalized with anthrax infection. However, during the recent bioterrorism-related anthrax events, more than 20 cases of cutaneous and inhalational anthrax were caused by contact with letters containing spores, suggesting that the risk of acquiring the disease from fomites might be higher than was previously realized.[1-3] Spores such as those found in the Hart Senate Office Building may have been weaponized to permit them to spread more easily. We have no data on the risks of person-to-person transmission or reaerosolization of these spores. This information will be critical for defining guidelines for infection control.

Decontamination of skin and clothing is recommended after a release of anthrax in order to reduce the risk of cutaneous disease, but such decontamination may present logistical difficulties.[1,4] If victims are not decontaminated before they go to the hospital, health care workers may be

exposed to anthrax spores and may thus be at risk for cutaneous, and possibly even inhalational, infection.

The recent cases of bioterrorism-related anthrax are forcing us to rethink the likelihood of patient-to-patient transmission and secondary aerosolization. To prevent the spread of anthrax spores to hospital workers, it may be prudent to use contact precautions for all patients who have been exposed to anthrax until they have been decontaminated. Isolation to prevent the spread of airborne spores should also be considered until more data on secondary aerosolization are available. This more stringent standard of care will help protect all hospital personnel.

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To the Editor: The terminal phase of anthrax results from toxemia. Once toxemia has reached a certain level, antibiotic therapy is no longer effective, since it does not lower the blood toxin level. The blood itself becomes toxic, in that sterile serum is lethal when injected into animals. Since pulmonary anthrax is usually well along on its pathologic course at the time of presentation, it is unlikely that antibiotic therapy alone can effect a cure.

When a patient presents with a blood toxin level approaching the lethal level, should complete blood replacement be used to lower the blood toxin level to a sublethal level so that the antibiotics can have a chance to work? The infused blood could contain an appropriate level of antibiotic, although there is still a possibility that the lysis of bacteria might increase the toxin level. Blood replacement might be used to buy time by lowering toxin levels to a point at which antibiotic therapy could be effective.

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To the Editor: Dr. Swartz states that person-to-person transmission of anthrax has not been reported. We are aware of several published reports describing person-to-person transmission of cutaneous anthrax, including anecdotal reports,[1,2] a case report,[3] and an investigation of an outbreak.[4] Two of these reports described nosocomial acquisition by a health care worker — in one case, a nursing orderly who contracted anthrax while dressing the lesion of a patient,[1] and in the other, an "unqualified general worker" who contracted anthrax after handling the soiled dressing of a patient with a new case of cutaneous anthrax.[2] A case series from Mexico included a case of skin infection on a baby's elbow that was thought to have been acquired from an infection on the mother's finger.[3] Finally, an investigation of an anthrax outbreak in India included the report of two cutaneous cases that occurred 40 and 60 days after the death of the first infected animal.[4] The authors concluded that these were probably due to human-to-human transmission, since in all other cases, cutaneous lesions appeared 1 to 13 days after the patient had handled a sick animal or eaten contaminated meat.

The standard precaution of using gloves to touch nonintact skin should prevent the transmission of cutaneous anthrax to health care workers. For added protection, we have recommended that contact precautions be used with patients with cutaneous anthrax.[5] As Dr. Swartz notes, potentially contaminated bandage material should be handled as regulated waste. We are unaware of any reports of person-to-person transmission of inhalational anthrax.

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Dr. Swartz replies:

To the Editor: Drs. McGovern and Norton question the basis of the recommendation that débridement of cutaneous lesions of anthrax be avoided and point out that eight patients with such lesions in the recent outbreak underwent biopsy uneventfully. The recommendation for avoidance of incision and débridement dates back to the era before antibiotics. The prominent localized perilesional edema has sometimes misleadingly suggested abscess formation and led to attempts at incision and drainage, which may have contributed to the bacteremia that occasionally complicates cutaneous anthrax. Performing a biopsy of the skin while simultaneously administering antibiotics, as was done during the recent outbreak, would entail minimal risk while allowing prompt diagnosis.

Drs. Lo Re and Fishman express concern about person-to-person transmission or reaerosolization of weaponized *B. anthracis* spores after a bioterrorism-related release. They are concerned that if victims are not decontaminated be-

fore being hospitalized, they may serve as a source of infection for health care workers. They advocate the use of contact precautions for patients who have been exposed to anthrax. Certainly, prompt decontamination of the environment, including skin and clothing, after a known release of *B. anthracis* spores is indicated. However, persons with cutaneous or inhalational anthrax would present some days after exposure and are infected with the vegetative forms of the organism, which are much less likely to be a source of person-to-person spread. Nonetheless, if heavy contamination of skin and clothing has occurred and initial decontamination has not been performed, reaerosolization and person-to-person spread are possible. In the recent outbreak, the time of exposure was known only in retrospect, which precluded prompt decontamination. Nonetheless, secondary cases among family contacts were not reported.

Ms. King raises the question of exchange transfusion in the late stage of inhalational anthrax as a means of preventing toxin-related death before antimicrobial action can take effect. The amount of tissue-bound toxin that would be present at this point and the likely hemodynamic compromise would probably limit the likelihood of success. A potent antitoxic antiserum or the recently developed inhibitor of anthrax toxin that binds to the heptameric protective antigen (PA) and blocks its interaction with edema factor (EF) and lethal factor (LF) may be more fruitful future approaches.[1]

Drs. Weber and Rutala refer to a few anecdotal reports suggesting person-to-person spread of cutaneous anthrax. Several of these reports were from areas (Africa and India) where the disease is endemic and where infection may have spread from a more conventional source. More convincing is the case in Mexico of skin infection on a baby's elbow that could have been acquired from an infection on the mother's finger. However, the rarity of these reports should be emphasized. Drs. Weber and Rutala agree that the use of standard precautions (including the use of gloves for contact with nonintact skin) should prevent the transmission of cutaneous anthrax to health care workers, but they would take the added step of implementing contact precautions for all patients with cutaneous anthrax.

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Cutaneous Anthrax Infection

To the Editor: Like many other clinicians, we were disheartened by the report of the diagnosis of cutaneous anthrax in a seven-month-old child (Nov. 29 issue).[1] However, what we found most distressing about this and other cases was that the initial diagnosis was envenomation by the brown recluse spider, *Loxosceles reclusa*. Although envenomation by this spider produces a necrotic lesion that may be mistaken for cutaneous anthrax, there are some critical differences that can help to guide future evaluations.

Loxosceles spiders prefer warm temperatures, and they are not native to the northern half of the United States.[2] In fact, no spider causing necrotic lesions is known to live in New York City. Furthermore, as the spider's name implies, these spiders are most commonly found hidden in woodpiles or barns — areas that are not typically visited by small children, as evidenced by the fact that few case series have included small children.[3,4]

Examination of the patient with a loxosceles bite generally reveals a painful blister, which may develop a dark purple coloration, with subsequent central necrosis of the lesion.[3] Unlike such bites, the lesions associated with cutaneous anthrax are often painless. The substantial edema and regional adenopathy that are characteristic of cutaneous anthrax are generally absent in patients with loxosceles envenomation.[5] Thus, despite some superficial similarity, a painless, edematous, necrotic lesion with local adenopathy in a person in the northeastern United States, especially in the colder months, is not likely to represent necrotic arachnidism.

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The authors reply:

To the Editor: The purpose of this Image in Clinical Medicine was to present an example of early cutaneous anthrax, since most reports show older, necrotic lesions. Because of space limitations, we did not discuss the differential diagnosis or other important issues involved in this complicated case.

We agree that the painless nature of the lesion was not typical of the bite of a brown recluse spider and that necrotic arachnidism in an infant in Manhattan is very unlikely. However, we could not rule out this possibility. Although loxosceles spiders are most highly concentrated in the south central United States, loxosceles species have been identified in virtually every state in the continental United

States,[1] and according to one spider expert, a "cousin" of the brown recluse spider, *L. refuscens,* had recently been sighted in the New York area. The family's car had recently been in regions inhabited by loxosceles species, and we postulated that a spider might have hidden in the infant's stroller or in the family's belongings. Although loxosceles bites are most common in the summer, a second peak can occur when victims unpack boxes and resume wearing stored winter clothing in which the spider may be hiding.[2] Furthermore, life-threatening hemolysis, thrombocytopenia, disseminated intravascular coagulation, hyponatremia, and acute renal failure developed in this infant, and all of these complications have been well described in patients with loxosceles envenomation.[1,2] A putative brown recluse spider bite[1,2] was the initial working diagnosis; since there is no specific antidote for such bites, the patient received antibiotics, corticosteroids, and supportive care, which was the appropriate therapy, even in retrospect.

At the time, anthrax in a seven-month-old child in Manhattan seemed nearly impossible. In fact, between 1984 and 2000, only five cases of cutaneous anthrax were reported in this country, and none of these occurred in children.[3,4] During this child's hospitalization, the first case of cutaneous anthrax in New York City was reported. The correct diagnosis in the child was then rapidly confirmed. The constellation of systemic complications is highly unusual in a patient of any age with cutaneous anthrax, and such complications have never been reported in a child, even in countries where anthrax is endemic.[5] Fortunately, the infection responded well to therapy, and the child recovered fully.

We are certainly wiser now than we were before September 11, 2001. A full case report of this infant's illness has been published, including serial photographs of the evolving lesion.[5] The early recognition of anthrax is crucial in patients of all ages.

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Sudden Death Due to Cardiac Arrhythmias

To the Editor: Spironolactone should be added to Table 2 of the article by Huikuri et al. (Nov. 15 issue)[1] as an intervention that may prevent sudden death from cardiac causes. In the Randomized Aldactone Evaluation Study,[2] patients with New York Heart Association class III or IV congestive heart failure who were randomly assigned to receive daily spironolactone had a lower risk of sudden death than patients who were randomly assigned to receive placebo (relative risk, 0.71; 95 percent confidence interval, 0.54 to 0.95; P=0.02). Possible mechanisms of this protective effect include potentiation of diuretic-induced hypokalemia as well as neurohormonal interactions.[2]

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1. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001;345:1473-82.
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To the Editor: The interesting review article on sudden death due to cardiac arrhythmias by Huikuri and colleagues did not comment on n−3 fatty acids as useful agents for the primary prevention of sudden death. These naturally occurring compounds are underused in this country and could potentially save thousands of lives each year.

Large, randomized prospective trials have shown that fish[1] or fish-oil capsules,[2] which provide approximately 1 g of n−3 fatty acids daily, can reduce the risk of sudden death by 50 percent in persons who have had a myocardial infarction. These fatty acids stabilize the electrical activity of cardiac myocytes by inhibiting membrane ion channels and prolonging the relative refractory period.[3] They also exert an antiarrhythmic action by increasing heart-rate variability.[4]

In addition to beta-blockers, n−3 fatty acids should be considered to be accepted therapeutic agents for preventing sudden death in persons who have had a myocardial infarction.

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The authors reply:

To the Editor: Dr. Berlin suggests that spironolactone and Dr. Goldstein proposes that n−3 fatty acids should be

included on the list of accepted therapeutic agents for preventing sudden death from cardiac causes. Indeed, two randomized trials have shown that fish[1] or fish-oil capsules[2] can reduce the risk of the combined end point of death, myocardial infarction, and stroke among patients with a prior myocardial infarction. In the Randomized Aldactone Evaluation Study,[3] spironolactone lowered the risk of death among patients with heart failure. Subanalyses of the results of these trials have also suggested that both n−3 fatty acids and spironolactone may reduce the risk of sudden death.

Despite these promising results, there are some shortcomings in the designs of these trials that prevent the generalization of the concept that these agents have a definite role in the primary prevention of sudden death from arrhythmia. First, none of these trials included sudden death from cardiac causes as a primary end point, and therefore, the studies were not powered accordingly. Second, there were no prespecified definitions of sudden death from cardiac causes in any of these trials, and only one end-point committee defined the mode of death. In fact, a recent beta-blocker study[4] was the first drug trial that paid specific attention to the definition of sudden death from cardiac causes. On the basis of the results of that trial and concordant information from a subanalysis of several other beta-blocker trials, we concluded that only in the case of beta-blocking drugs was there sufficient evidence to warrant their inclusion as a recommended treatment for the primary prevention of sudden death from cardiac causes.

Definitive evidence from prospective trials should be a requirement before any therapeutic strategy is widely recommended and accepted. Any new preventive strategies that can decrease the worldwide problem of sudden death from cardiac causes will be welcomed, but the overall and individual effects[5] must first be proved by means of carefully planned and executed clinical trials.

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Red Pepper and Functional Dyspepsia

To the Editor: Functional dyspepsia is a common and distressing chronic digestive disorder of unknown cause.[1,2] We examined the effect of treatment of functional dyspepsia with capsaicin (trans-8-methyl-*N*-vanillyl-6-nonenamide), a component of red-pepper (*Capsicum annum*) powder. Capsaicin selectively impairs the activity of nociceptive C fibers carrying pain sensations to the central nervous system[3] and has been shown to relieve pain of cutaneous and mucosal origin.[4]

After the exclusion of patients with gastroesophageal reflux and irritable bowel syndrome, we monitored 30 patients with functional dyspepsia[2] for two weeks while they were receiving no medications. Fifteen patients were randomly assigned in a double-blind manner to receive 2.5 g of red-pepper powder a day (contained in capsules taken before each of three meals) for five weeks, and the other 15 were randomly assigned to receive placebo capsules. The capsaicin content was 0.7 mg per gram of red-pepper powder, as determined by means of high-performance liquid chromatography. A diary sheet was given to each patient to record daily symptom scores. The symptom scores obtained in the red-pepper group during the entire treatment period were compared with those obtained in the placebo

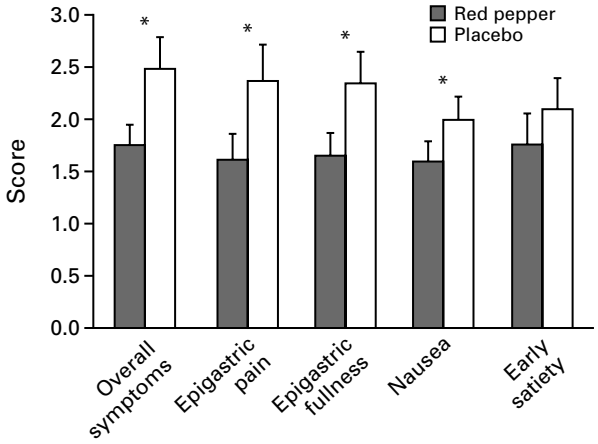

Figure 1. Mean (±SD) Scores for Overall and Individual Symptoms during the Entire Treatment Period with Red Pepper or Placebo.

Higher scores indicate more severe symptoms. Asterisks indicate a significant difference ($P<0.05$) between the groups. The difference between groups in the early-satiety score was at the borderline of significance ($P<0.06$); the results of analyses of other symptoms considered in the study, such as epigastric burning, bloating, and burping, were not included in the figure, because they did not differ significantly between the two groups.

TABLE 1. BASE-LINE AND WEEKLY SCORES FOR OVERALL AND INDIVIDUAL SYMPTOMS IN THE RED-PEPPER GROUP AND THE PLACEBO GROUP.*

SYMPTOM	BASE LINE	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
				score		
Overall symptoms						
Red-pepper group	3.29±0.6	2.80±0.8	1.95±0.7†	1.45±0.6†‡	1.30±0.6†‡	1.25±0.5†‡
Placebo group	3.42±0.7	2.85±0.6†	2.50±0.7†	2.35±0.6†	2.35±0.5†	2.40±0.6†
Epigastric pain						
Red-pepper group	2.95±0.6	2.66±0.8	1.81±0.8†	1.25±0.6†‡	1.20±0.5†‡	1.15±0.5†‡
Placebo group	3.10±0.7	2.59±0.6†	2.40±0.7†	2.30±0.5†	2.24±0.6†	2.32±0.6†
Epigastric fullness						
Red-pepper group	2.98±0.7	2.55±0.7	1.85±0.7†	1.40±0.6†‡	1.25±0.4†‡	1.20±0.5†‡
Placebo group	3.11±0.6	2.65±0.6†	2.39±0.6†	2.25±0.5†	2.26±0.6†	2.20±0.6†
Nausea						
Red-pepper group	2.65±0.5	2.49±0.6	1.80±0.7†	1.29±0.5†‡	1.22±0.6†‡	1.19±0.5†‡
Placebo group	2.79±0.6	2.23±0.7†	2.07±0.6†	1.88±0.5†	1.91±0.5†	1.91±0.6†

*Plus–minus values are means ±SD. Higher scores indicate more severe symptoms. Both the overall and individual symptom scores of patients treated with red pepper were significantly lower than base-line values from the second week onward, whereas symptom scores in the placebo group decreased significantly beginning in the first week. However, beginning in the third week all individual and global scores in the red-pepper group were significantly lower than those in the placebo group.

†$P<0.05$ for the comparison with base-line values.

‡$P<0.05$ for the comparison with the placebo group.

group, and the mean weekly scores in both groups were plotted against time and compared between groups and with the corresponding base-line value obtained the week before treatment began. Parametric tests (analysis of variance for repeated measurements and Student's t-test for paired data) and a nonparametric test (the Mann–Whitney U test) were used as appropriate.

Two of the 15 patients in the red-pepper group discontinued the trial because of epigastric pain, and 1 patient in the placebo group stopped treatment for other reasons ($P=1.00$ by Fisher's exact test). The overall symptom scores as well as the scores for epigastric pain, epigastric fullness, and nausea during the entire treatment period were significantly lower in the red-pepper group than in the placebo group (Fig. 1). The weekly scores in the red-pepper group were significantly lower than those in the placebo group beginning in the third week of treatment (Table 1) and, in the last week of treatment, had decreased by a mean of approximately 60 percent, whereas those in the placebo group had decreased by approximately 30 percent. The administration of red pepper was more effective than placebo in decreasing the intensity of dyspeptic symptoms, probably through a capsaicin-induced desensitization of gastric nociceptive C fibers. Although larger trials with standardized materials are needed, capsaicin could represent a potential therapy for functional dyspepsia.[5]

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