

## CORRESPONDENCE



## Thrombolytic Therapy in Patients with Submassive Pulmonary Embolism

**TO THE EDITOR:** Konstantinides et al. (Oct. 10 issue)<sup>1</sup> evaluated the role of alteplase in patients with submassive pulmonary embolism. Their findings will be regarded by many as definitive evidence in support of the use of thrombolytic agents in such patients. However, a review of the study design, particularly the end points chosen, shows that the data do not support the authors' conclusions.

The only primary end point to show significant improvement was an escalation of treatment for clinical deterioration — nearly always meaning treatment with open-label alteplase, the drug used in the intervention group. The decision to escalate treatment was made by clinicians, who were permitted to break the randomization code first; thus, the primary end point in a given case could be determined by an unblinded provider. Escalation of treatment would have been unlikely in a patient with clinical deterioration who was in the alteplase group but would have been likely in a patient with similar deterioration who was in the placebo group.

The study suggests that the number needed to treat was nine; in other words, nine patients would have to be given alteplase to avoid treatment escalation (i.e., use of open-label alteplase) in one patient. In view of the 1 percent risk of major hemorrhage with thrombolysis,<sup>2</sup> avoiding open-label use in one patient hardly justifies preemptive use of the drug in many more patients.

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1. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347:1143-50.

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**TO THE EDITOR:** Konstantinides et al. purportedly demonstrate a significant clinical benefit of thrombolysis in patients with submassive pulmonary embolism. However, we believe a more subtle conclusion can be reached.

The authors' primary end point was a composite of clinical deterioration requiring an escalation of treatment and death. Although the incidence of the composite end point differed significantly between the study groups, the difference appears to be due to escalation of treatment in a larger number of patients in the placebo group. This escalation can be entirely accounted for by the use of secondary thrombolysis in patients whose clinical condition was thought to be deteriorating.

The authors state, "The trial protocol permitted breaking of the randomization code if additional therapy had to be provided on an emergency basis to a patient whose condition was deteriorating." In other words, if a patient's condition was deteriorating, one could determine whether the patient had received thrombolytic therapy or placebo and thereafter decide whether to give the patient alteplase. Most reasonable clinicians who realized that a patient with clinical deterioration had received placebo would administer thrombolytic agents. Thus, the unblinding of randomization status undermines the validity of the statistically significant difference in the end point between the groups.

Although this study does not demonstrate a significant difference in rates of major bleeding, a finding that supports the safety of alteplase, the principal conclusion that can be drawn from the study is that the use of alteplase for submassive pulmonary

embolism decreases the frequency of the use of thrombolytic therapy later in the hospital course.

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**TO THE EDITOR:** Inadequate anticoagulation with heparin may explain the apparent superiority of alteplase over placebo for the treatment of submaximal pulmonary embolism, as reported by Konstantinides et al. The mean activated partial-thromboplastin time was significantly lower in the placebo group than in the alteplase group during the first six hours after randomization. Previous clinical trials have established the superiority of a weight-based heparin nomogram over the protocol used by Konstantinides et al. (a bolus of 5000 units of unfractionated heparin, followed by 1000 units per hour).<sup>1</sup>

Patients treated for venous thromboembolism who have subtherapeutic partial-thromboplastin times during the first 24 hours of treatment have an increased risk of recurrent events.<sup>2</sup> It would be interesting to know how many patients who reached the primary end point in the trial conducted by Konstantinides et al. had subtherapeutic partial-thromboplastin times.

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**TO THE EDITOR:** The most striking finding in the double-blind, randomized trial reported by Konstantinides et al. is that of the 118 patients treated with alteplase, only 1 had major bleeding and none had intracranial hemorrhage. These results are in sharp contrast to those reported by other groups. As Goldhaber notes in the accompanying Perspective,<sup>1</sup> in the International Cooperative Pulmonary Embolism Registry, the incidence of intracranial hemorrhage in 304 patients receiving thrombolytic therapy was 3.0 percent. In a 1997 review that my colleagues and I reported,<sup>2</sup> the incidence of intracranial hemorrhage in 559 patients treated with re-

combinant tissue plasminogen activator was 2.1 percent, and the incidence of fatal intracranial hemorrhage was 1.6 percent. In Levine's review of 227 patients with pulmonary embolism who were treated with recombinant tissue plasminogen activator, the incidence of major hemorrhage was 8.4 percent, and the incidence of fatal hemorrhage was 2.2 percent.<sup>3</sup> The report by Konstantinides et al. is the only one in the literature in which the incidence of major bleeding with heparin alone was higher than the incidence with heparin plus a thrombolytic agent. Was this exceptionally low incidence of major bleeding in patients treated with alteplase due to chance, or was it due to more stringent contraindications to thrombolytic therapy? Given the fact that the bleeding complications of thrombolytic therapy are the main deterrent to its more widespread use in patients with pulmonary embolism, this becomes a critical question. What percentage of the patients screened for this study were excluded because of a contraindication to thrombolytic therapy?

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**TO THE EDITOR:** The report by Konstantinides et al. emphasizes that treatment with alteplase, given in conjunction with heparin, may improve the clinical course of patients with acute submassive pulmonary embolism. However, the grading of pulmonary embolism remains unclear. The definition cited in the article fails to differentiate massive from submassive pulmonary embolism<sup>1</sup>; presumably, submassive pulmonary embolism is characterized by right ventricular dysfunction or pulmonary hypertension without hemodynamic instability.

Pulmonary emboli have a wide spectrum of clinical severity and differ markedly in size and physiological effects. Right ventricular dysfunction appears to reflect a large thrombotic burden. We believe that Konstantinides et al. should have reported the results of lung scanning, spiral computed tomography (CT), or pulmonary angiography, since these studies provide quantification of the embolic load. Finally, how did the investigators ensure that right

ventricular dysfunction or pulmonary hypertension did not predate the embolic event?

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**THE AUTHORS REPLY:** Ashton et al. and Gunn and Tierney question the validity of our combined end point, which includes the need for rescue thrombolysis. In our opinion, their concern is unjustified. In particular, the assumption that late thrombolysis was likely only in the placebo group is incorrect. Patients from both groups were eligible for and did receive emergency thrombolysis after the code had been broken, since, as shown in Figure 1 of our article, deterioration often occurred several hours or days after the administration of the study medication. We clearly stated in our article that mortality rates did not differ between the treatment groups. However, severe clinical or hemodynamic deterioration (as defined in the Methods section) requiring emergency thrombolysis is also an important adverse event and clinical end point. Since treatment with alteplase significantly reduced the risk of reaching this end point, we concluded that it can improve the outcome in patients with submassive pulmonary embolism. It would have been unacceptable to prohibit or ignore escalation of treatment in the study protocol.

As shown in Figure 2 of our article, the difference in activated partial-thromboplastin times during the first six hours was mostly due to high, supratherapeutic partial-thromboplastin values in the alteplase group rather than low values in the placebo group. Of the patients who reached the primary end point, only one patient in the alteplase group and four patients in the placebo group had subther-

apeutic partial-thromboplastin times at six hours. All these patients had therapeutic values six hours later. The heparin regimen complied with medical statements of the American Heart Association at the time our study was designed.

The absence of intracranial hemorrhage in our study is similar to the findings of several trials of thrombolysis cited by Dalen.<sup>1</sup> Although minor differences (in absolute numbers) between prospective trials involving patients with pulmonary embolism may be due to chance, in view of the relatively small numbers of patients included, the difference between the results of our trial and the results of previous registry studies<sup>2,3</sup> underscores the importance of strict exclusion criteria based on the contraindications to thrombolysis.

In our study population, which was clearly defined in the Methods section of our article, submassive pulmonary embolism was characterized by right ventricular dysfunction or pulmonary hypertension without hemodynamic instability. The findings on lung scans or spiral CT scans were not reported because they have not been found to be directly correlated with right ventricular failure or with outcome. Finally, we have previously proposed the use of echocardiographic criteria to distinguish acute from subacute right ventricular pressure overload due to pulmonary embolism.<sup>4</sup>

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## Inhibition of Tumor Necrosis Factor $\alpha$ and Ankylosing Spondylitis

**TO THE EDITOR:** In a recent multicenter trial, Gorman et al. (May 2 issue)<sup>1</sup> found that 80 percent of patients with active ankylosing spondylitis had a favorable response to etanercept. Equivalent results

are obtained with infliximab.<sup>2</sup> Data on uveitis are still lacking. We report a case of severe uveitis in a 45-year-old man that improved with infliximab.

In 1986, the patient was given a diagnosis of

HLA-B27–positive ankylosing spondylitis. Since 1993, he had had recurrent bilateral anterior uveitis, leading to functional blindness of the right eye despite the use of antiinflammatory drugs, including corticosteroids. When he was seen in May 1996 because of persistent joint and eye inflammation, he was treated with 60 mg of prednisone per day and 15 mg of methotrexate per week; the dose of prednisone was then tapered. Despite an increase in the dose of methotrexate up to 25 mg per week, bilateral uveitis relapsed. Methotrexate treatment was discontinued in April 2001 because of lack of efficacy and alcoholic hepatitis.

In July 2001, a new relapse led to the initiation of treatment with intravenous cyclophosphamide at a monthly dose of 1000 mg. In January 2002, after six pulses of cyclophosphamide, severe uveitis occurred in the left eye, with a decrease in visual acuity from 10/10 to 5/10 and cystoid macular edema. After three pulses of methylprednisolone, 5 mg of infliximab per kilogram of body weight was administered on day 1, day 8, day 15, and at eight weeks. Cystoid macular edema decreased, visual acuity improved to 10/10, and ocular inflammation disappeared. The dose of oral prednisone was regularly and rapidly reduced to 25 mg per day without relapse. These findings suggest that inhibitors of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) could be effective in the treatment of uveitis associated with ankylosing spondylitis, as they are for uveitis associated with Crohn's disease<sup>3</sup> or Behçet's disease.<sup>4</sup>

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**TO THE EDITOR:** The role of TNF- $\alpha$  in ankylosing spondylitis is better understood than its role in rheumatoid arthritis. The predominant inflammatory cell at sites of acute enthesitis and osteitis is

the macrophage, and a high level of expression of TNF- $\alpha$  has been shown at these sites. Animal models that demonstrate the efficacy of inhibiting tumor necrosis factor (TNF) are arguably better models for the pathogenesis of ankylosing spondylitis than for that of rheumatoid arthritis, and overexpression of TNF leads to a disease reminiscent of ankylosing spondylitis.<sup>1</sup> Evidence in the article by Gorman et al. suggests that up to 80 percent of patients with ankylosing spondylitis have a response to etanercept, as compared with patients with rheumatoid arthritis, who may not have a response — suggesting that TNF- $\alpha$  has a more central role in the pathogenesis of ankylosing spondylitis. We do not believe it is possible to extrapolate observations from peripheral synovial tissue to the enthesitis that characterizes spinal disease in ankylosing spondylitis. In addition, synovitis may be secondary to the release of TNF from these lesions.<sup>2</sup>

In contrast to the report of Gorman et al., we reported that fatigue improved by 57 percent in patients with ankylosing spondylitis who were treated with etanercept for 24 weeks, and this improvement was mirrored by improvement in spinal inflammatory lesions as determined by magnetic resonance imaging.<sup>3</sup> With regard to the many unanswered questions pertaining to the use of biologic agents in patients with ankylosing spondylitis, the pivotal issue is whether suppression of inflammation prevents new bone formation and ankylosis, the chief cause of chronic disability in patients with this disease.

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**THE AUTHORS REPLY:** Regarding the report by Dr. Asli and colleagues of the successful treatment with infliximab of a case of HLA-B27–associated uveitis: although randomized, controlled studies of anti-TNF therapies for this indication are lacking,

the use of these agents for the treatment of inflammatory eye disease is being increasingly reported.<sup>1,2</sup>

In an open-label study of etanercept in the treatment of spondyloarthritis, Dr. Marzo-Ortega and colleagues reported substantial improvement in fatigue. In their study, fatigue was measured by a single question from the Bath Ankylosing Spondylitis Activity Index.<sup>3</sup> Responses to this question about fatigue correlate significantly with responses to the eight components of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) that we used,<sup>4</sup> in six of which there was significant improvement with etanercept therapy in our trial. There may be several suitable measures of fatigue in patients with ankylosing spondylitis,<sup>4</sup> but at the time our study was initiated, no instrument had been deemed relevant by the Assessments in Ankylosing Spondylitis Working Group.<sup>5</sup>

We would like to make a correction to the response rate among etanercept-treated patients in our trial. One patient in the etanercept group during the randomized portion of the study was inadvertently classified as having had a response at four months. Although the patient had greater than 20 percent improvement in the duration of morning stiffness (33 percent), nocturnal spinal pain (65 percent), patient's global assessment of disease activity (25 percent), and Bath Ankylosing Spondylitis Functional Index (49 percent), the swollen-joint score

had increased from 0 to 2 by the end of the study. According to the intention-to-treat principle with the last value carried forward, the percentage of patients in the etanercept group with a response to treatment (reported at the bottom of the left-hand column on page 1351, in Table 2, and in Figure 1 of our article) should be 75 percent instead of 80 percent, with a corrected P value of 0.01 by Fisher's exact test (two-tailed). We regret the error.

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## Antimicrobial Peptides in the Skin

**TO THE EDITOR:** Ong et al. (Oct. 10 issue)<sup>1</sup> described a lack of induction of human  $\beta$ -defensin 2 (HBD-2) and the cathelicidin LL-37 in atopic skin disease as compared with psoriasis, yielding a plausible explanation for the superinfection by gram-positive strains seen in neurodermatitis. In the accompanying editorial,<sup>2</sup> Zasloff asks whether other disorders may also be related to a defensin deficiency; Crohn's disease, in contrast to ulcerative colitis, may be due to deficient induction of HBD-2.<sup>3,4</sup>

Several arguments suggest that there is a deficiency of the mucosal antibacterial barrier in Crohn's disease. Adherent strains of *Escherichia coli* are frequently encountered in the ileal mucosa of patients with Crohn's disease, suggesting that the microflora have a pathogenic role. The colonic mucosa of patients with inflammatory bowel disease is covered with adherent bacteria composed of normal flora, and the immune response is apparently directed against these bacteria. Patients with Crohn's

disease have reduced amounts of HBD-2 in the colonic mucosa, according to studies of messenger RNA and immunohistochemical analysis.<sup>4</sup> Thus, this feature is shared by atopic dermatitis and Crohn's disease. Therefore, both the deficient HBD-2 induction and the defective NOD2 (*CARD15*) gene associated with Crohn's disease<sup>5</sup> suggest that Crohn's disease is due to a disturbance in innate, not adaptive, immunity.

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**THE AUTHORS REPLY:** The comments of Fellermann and colleagues highlight an important issue in the rapidly advancing field of antimicrobial peptides. We agree with their speculation that disease in organ systems other than the skin may be associated with an abnormality in naturally occurring peptide antibiotics. In particular, the gastrointestinal tract has provided many examples to support the importance of these molecules. Reduction of epithelial expression of both cathelicidin and  $\beta$ -defensin 1 is mediated by microbial products of shigella species and has been suggested to be a virulence factor in this disease.<sup>1</sup> Mice lacking an enzyme critical to the activation of  $\alpha$ -defensins have a reduced ability to eliminate orally administered bacteria.<sup>2</sup> Pathogenic bacteria such as *Pseudomonas aeruginosa* and *Enterococcus faecalis* degrade LL-37 and inactivate it.<sup>3</sup> Such observations demonstrate that this aspect of the innate immune system is subject to inactivation at many levels.

However, it is premature to suggest that the pathogenesis of associated diseases involves only defects in innate immunity. As discussed in our article and the accompanying editorial, antimicrobial peptides interact with the host at many levels and influence cellular responses associated with adaptive immunity.<sup>4,5</sup> The multifunctional nature of peptides with antimicrobial activity, such as HBD-2 and the cathelicidins, suggest that any distinctions drawn between so-called “innate” and “adaptive” immunity are arbitrary. A deficiency of endogenous antimicrobials in atopic dermatitis or Crohn's disease may explain important aspects of the disorder, but it is likely to do so in the context of a coordinated immune response.

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**THE EDITORIALIST REPLIES:** Fellermann and colleagues suggest that recent data support a revision of our notion of Crohn's disease as a primary disorder of epithelial innate immunity rather than a primary dysfunction of adaptive immunity. The report by Ong et al. supports the hypothesis that atopic eczema is a primary allergic reaction with a type 2 helper T cell–like character, associated with secondary suppression of antimicrobial-gene expression, which as a consequence leads to bacterial infections of the skin. In the case of Crohn's disease, the cause of the depressed expression of HBD-2 by the gut epithelium observed by Wehkamp et al.<sup>1</sup> remains to be elucidated. It could well be that Crohn's disease results from a genetic defect in a pathway involved, directly or indirectly, in the expression of epithelial HBD-2. Recent data, for example, suggest that NOD2, an intracellular macrophage protein (one that resembles a plant microbe sensor), malfunctions in some persons with Crohn's disease<sup>2</sup>: since macrophages secrete proinflammatory cytokines that induce epithelial defensins, normal crosstalk between macrophages and the epithelium might be defective in this cohort. Clinical studies also suggest that certain microorganisms can suppress antimicrobial-gene expression in the human gut epithelium,<sup>3</sup> supporting the alternative hypothesis that HBD-2 suppression might be an acquired, infection-based defect in innate immunity.

If Crohn's disease were found to be a primary disorder of the innate immune defenses of the epithelium, the effect on treatment would be profound. Current treatment focuses on suppression of the inflammatory state. If the primary defect is a failure of expression of gut epithelial antimicrobial peptides, therapy could be directed at safely stimulating the expression of these microbicidal agents with inducers, such as isoleucine, as previously suggested.<sup>4</sup>

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## Otitis Media

**TO THE EDITOR:** In the article on otitis media (Oct. 10 issue),<sup>1</sup> Hendley's conclusions about the moderate value of antibiotics in acute otitis media are based largely on the results of published meta-analyses.<sup>2-4</sup> Selecting studies for inclusion in meta-analyses requires consideration of methodologic issues. Among these is the definition of acute otitis media. Hendley stringently defines acute bacterial otitis media,<sup>1</sup> but if studies evaluating the effect of antibiotic therapy have weak definitions (allowing the inclusion of children more likely to have otitis media with effusion than acute otitis media), the response in recipients of placebo will not differ much from that in recipients of an antibiotic. None of the three meta-analyses cited used a stringent definition of acute otitis media.

In the study cited as support for watchful waiting as a management strategy for acute otitis media,<sup>5</sup> the dose of amoxicillin was 125 mg three times daily for all children. For a 10-kg child, this dose amounts to 38 mg per kilogram of body weight per day; for a 30-kg child, 12 mg per kilogram per day. In essence, the investigators were comparing placebo with placebo, especially in older children. The evidence in the literature is not sufficient to support the conclusion that antibiotics have a minimal role in most cases of acute otitis media.

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**DR. HENDLEY REPLIES:** Wald correctly points out that all trials comparing antibiotics and placebo have used "weak definitions" of otitis media as criteria for enrollment, rather than a "stringent definition" of acute bacterial otitis media (i.e., a bulging tympanic membrane with purulent fluid behind it, or a "pus drum," as shown in Fig. 2B in the article). I recommend immediate treatment of this form of bacterial otitis media with high-dose amoxicillin, whereas the strategy of delayed prescription of an antibiotic would be my choice for all other episodes of acute otitis media.

Wald also notes that in the cited study of the delayed-prescribing strategy for otitis media,<sup>1</sup> the dose of amoxicillin was low, particularly in older children. However, the critical finding in the study was that three fourths of the parents in the delayed-prescribing group did not even pick up the antibiotic prescription because of realization that their children's condition was improving by three days with acetaminophen alone. This strategy appears to be a reasonable means to select the small proportion of children (13 percent) with acute otitis media who will benefit from antibiotic therapy.

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## *Helicobacter pylori*

**TO THE EDITOR:** The review article by Suerbaum and Michetti on *Helicobacter pylori* infection (Oct.

10 issue)<sup>1</sup> lists dual therapy with ranitidine bismuth citrate and clarithromycin as a treatment

**Table 1. Rates of Treatment Failure and Emerging Resistance to Clarithromycin with Dual- and Triple-Therapy Regimens for *Helicobacter pylori* Infection.\***

Regimen	Treatment Failure		Emerging Resistance	
	Patients with Susceptible Isolates before Treatment	Resistant Isolates before Treatment	All Treated Patients†	Patients with Treatment Failure‡
	no./total no. (%)	no./total no.	no./total no. (%)	no./total no.
<b>Dual therapy</b>				
Ranitidine bismuth citrate, 400 mg twice a day, plus clarithromycin, 500 mg twice a day for 14 days, then ranitidine bismuth citrate, 400 mg twice a day for 14 days	19/125 (15.2)	19/20	12/120 (10.0)	12/14
Ranitidine bismuth citrate, 400 mg twice a day, plus clarithromycin, 500 mg 3 times a day for 14 days, then ranitidine bismuth citrate, 400 mg twice a day for 14 days	26/124 (21.0)	16/17	14/116 (12.1)	14/18
Omeprazole, 40 mg daily, plus clarithromycin, 500 mg 3 times a day for 14 days, then omeprazole, 20 mg daily for 14 days	36/108 (33.3)	4/4	26/99 (26.3)	26/27
<b>Triple therapy</b>				
Omeprazole, 20 mg twice a day, plus amoxicillin, 1 g twice a day, plus clarithromycin, 500 mg twice a day for 10 days, then omeprazole, 20 mg daily for 18 days	18/171 (10.5)	10/14	3/163 (1.8)	3/10
Lansoprazole, 30 mg twice a day, plus amoxicillin, 1 g twice a day, plus clarithromycin, 500 mg twice a day for 10 days	2/4 (4.8)	3/4	1/42 (2.4)	1/2
Lansoprazole, 30 mg twice a day, plus amoxicillin, 1 g twice a day, plus clarithromycin, 500 mg twice a day for 14 days	7/112 (6.2)	11/17	0/105 (0)	0/0
Esomeprazole, 40 mg daily, plus amoxicillin, 1 g twice a day, plus clarithromycin, 500 mg twice a day for 10 days	20/182 (11.0)	16/29	2/168 (1.2)	2/6

\* Data are based on the package inserts for clarithromycin and esomeprazole.<sup>3,4</sup>

† Treated patients are defined as the number of patients with a susceptible isolate (defined as a minimal inhibitory concentration [MIC]  $\leq 0.25 \mu\text{g}$  per milliliter) before treatment who were found to be *H. pylori*-positive after treatment, with a resistant isolate (defined as a MIC  $\geq 2 \mu\text{g}$  per milliliter for omeprazole, amoxicillin, and clarithromycin and  $>1 \mu\text{g}$  per milliliter for esomeprazole, amoxicillin, and clarithromycin), divided by the number of patients with a susceptible isolate before treatment minus those without post-treatment MICs.

‡ Patients with treatment failure are defined as the number of patients with a susceptible isolate (defined as a MIC  $\leq 0.25 \mu\text{g}$  per milliliter) before treatment who were found to be *H. pylori*-positive after treatment, with a resistant isolate (defined as a MIC  $\geq 2 \mu\text{g}$  per milliliter for omeprazole, amoxicillin, and clarithromycin and  $>1 \mu\text{g}$  per milliliter for esomeprazole, amoxicillin, and clarithromycin), divided by the number of patients found to be *H. pylori*-positive after treatment with any MIC result.

option approved by the Food and Drug Administration. Ranitidine bismuth citrate tablets for use in combination with clarithromycin to eradicate *H. pylori* infection in patients with an active duodenal ulcer were approved on August 8, 1996. However, in 1999, Glaxo Wellcome voluntarily withdrew the product from the U.S. market.

Dual-therapy regimens containing clarithromycin as the sole antimicrobial agent are less effective than approved triple-therapy regimens containing two antimicrobial agents, and the treatment guidelines issued by the American College of Gastroenterology no longer include dual-therapy regimens.<sup>2</sup> Moreover, dual-therapy regimens containing clarithromycin as the sole antimicrobial agent may limit future treatment options by inducing resistance. Rates of treatment failure and rates of emerging resistance to clarithromycin with dual- and tri-

ple-therapy regimens are shown in Table 1.<sup>3,4</sup> In summary, the potential for higher rates of emerging resistance to clarithromycin with dual-therapy regimens, as compared with triple-therapy regimens, should be taken into account when a treatment regimen is selected.

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**TO THE EDITOR:** The role of testing after treatment to eradicate *H. pylori* is growing in importance in clinical practice.<sup>1-3</sup> In their review of *H. pylori* infection, Suerbaum and Michetti state that stool antigen tests are suitable for follow-up of infection, provided that an eight-week interval is allowed after therapy. However, a prospective, multicenter study<sup>4</sup> showed that a positive result on the stool antigen test, performed just seven days after completion of therapy, identified patients in whom eradication of *H. pylori* infection had been unsuccessful. Such a test, with this timing, should be considered as a useful tool in assessing the outcome of treatment of *H. pylori* infection.

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## Changing Health Insurance Trends

**TO THE EDITOR:** The strategies presented by Galvin and Milstein (Sept. 19 issue)<sup>1</sup> are relevant to the current national dialogue; however, the authors neglected to consider models in which providers are paid on the basis of performance. Contrary to what the authors suggest, many insurers are effectively improving the quality of health care, while also achieving economic efficiencies, by gradually introducing innovative models for the reimbursement of providers on the basis of the quality of their output. This approach is so promising that a leading foundation issued a call for proposals for performance-based compensation models.<sup>2</sup>

After stating that “to date, a minority of consumers have used health care performance ratings as a basis for choosing providers,” the authors continue to believe that the provision to consumers of less complex and more timely information alone will suffice. In the past, public reports ranking physicians and medical groups according to their performance as determined by a nationwide analysis<sup>3,4</sup> resulted in no substantial change in the behavior of consumers or providers.

The authors fail to note the wide variation among providers in the adoption of evidence-based guidelines for the care of patients, and in general, in the current environment, there is no financial incentive to adopt such guidelines. The authors suggest that employers want to use the same approach in purchasing health care as they do in their core business in order to improve overall health care, but their

other vendors are paid, or retained, on the basis of the quality of their output. If the quality of a vendor's product is poor, this will be reflected in their payment. The pay-for-performance models deserve the attention of mainstream think tanks and policymakers, who can encourage the use of reimbursement models that reward providers for high-quality medical care.

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**TO THE EDITOR:** I believe that in Iglehart's otherwise accurate summary of the current health insurance crisis (Sept. 19 issue),<sup>1</sup> he overinterprets Galvin and Milstein's remarks about large employers and the tilt toward defined-contribution insurance. As Martin and Gauthier state in a recent monograph, “Depending on the model implemented, defined contribution health benefits may lead to increased risk segmentation. An employer's risk

pool is almost certain to disperse if employees go into the individual market, where premiums for healthier and/or younger people are markedly lower than those for sicker and/or older people, who, in some cases, are unable to get coverage at all.”<sup>2</sup> But Iglehart is clearly correct in highlighting the importance of motivating consumers through appropriate mechanisms for copayment and co-insurance and empowering them through the provision of information on performance. As Robinson has pointed out, “Americans’ first-best health care preference is cost-unconscious choice, with some distant, unknown party footing the bill. When faced with the second-best trade-off between cost-conscious choice and no choice at all, however, Americans may grumble but select the former.”<sup>3</sup>

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**THE AUTHORS REPLY:** Paying differentially on the basis of performance is an emerging strategy of large employers and is one of the three purchasing principles of the Leapfrog Group.<sup>1</sup> It was omitted from our Sounding Board article only because of space constraints.

The National Health Care Purchasing Institute recently summarized approaches that purchasers and payers may take to reward providers for quality.<sup>2</sup> Although Dr. Legorreta is correct that there have been examples of health plans rewarding providers for quality, this has not been the case with Medicare or most insurers, and there is little evidence that the phenomenon is growing. Leapfrog employers will be insisting that the health insurers with whom they do business have pay-for-performance systems. Several new employer initiatives are under way that build on previous efforts but attempt to get clinicians more involved in designing the programs and defining the rewards.<sup>3</sup> Disseminating performance measures, engaging consumers, and rewarding clinicians for quality and efficiency are synergistic tactics in employers’ overall market

strategy for encouraging providers to cross the quality chasm.

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**MR. IGLEHART REPLIES:** My description of the defined-contribution model (also known as “consumer-driven” health insurance) was carefully couched to reflect its current status as a benefit option. I reported that these products are considered the first wave of more profound changes sought by employers who are searching for new ways to cap the expenses they incur in purchasing health insurance for their employees. I noted that, to date, “only a handful” of employers are offering this type of health benefit. I identified many of the few large firms that have added this option for coverage, raised a concern expressed by employers who are self-insured that this approach may be more, rather than less, expensive, and reported the misgivings of some analysts that these products could further fragment insurance risk pools. Dr. Lyons is entitled to his opinion, but I would not describe my account as an overinterpretation, but rather as a reality check.

More important, though, one should recognize that benefit offerings change rapidly as the (often conflicting) interests of employers and workers shift.<sup>1,2</sup> A recent report by Gabel and colleagues, based on interviews conducted in early 2002 with industry leaders and other stakeholders, estimated that 1.5 million Americans (less than 1 percent of the employer-coverage market) are being offered defined-contribution products.<sup>3</sup> But the authors added: “Many health plans and benefit consultants, however, see consumer-driven plans accounting for 20 percent of the market by 2005 and as much as 50 percent by 2007.”

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## Increased Prevalence of Sleep-Disordered Breathing among Professional Football Players

**TO THE EDITOR:** Sleep-disordered breathing is a clinical disorder consisting of apnea and hypopnea during sleep; it affects about 4 percent of the general population.<sup>1</sup> We examined sleep-disordered breathing in a group of National Football League players. We used a value of 0.5 on the multivariable apnea-prediction index, on the basis of data from eight randomly selected teams, to stratify players according to the risk of sleep-disordered breathing (high or low).<sup>2</sup> Players from both risk groups were randomly selected for overnight polysomnography, with oversampling from the high-risk group. Of a total of 302 players who could be evaluated (mean [ $\pm$ SD] age, 25.5 $\pm$ 2.7 years; body-mass index [the weight in kilograms divided by the square of the height in meters], 31.5 $\pm$ 4.6), 52 players gave written informed consent for full overnight polysomnographic studies. We used a conservative apnea-hypopnea index cutoff value of 10 to define sleep-disordered breathing.<sup>3</sup>

Offensive and defensive linemen accounted for 85 percent of the cases of sleep-disordered breathing (Table 1); linemen also had the largest neck circumference (19.1 $\pm$ 0.9 in. [48.5 $\pm$ 2.3 cm]) and highest body-mass index (36.6 $\pm$ 2.6). Both systolic blood pressure (129 $\pm$ 11 vs. 122 $\pm$ 9 mm Hg) and diastolic blood pressure (84 $\pm$ 9 vs. 77 $\pm$ 8 mm Hg) were significantly higher in the linemen than in all the other players ( $P$ <0.01). From these data, we estimate the prevalence of sleep-disordered breathing among all professional football players to be 14 percent overall and 34 percent within the high-risk group (Table 1). The estimated prevalence is higher than that found in a cross-sectional study of men of similar age,<sup>4</sup> and emphasizes the importance of physiology over physical conditioning as a risk factor for sleep-disordered breathing. Although young and ostensibly in excellent physical condition, profes-

sional football players have many of the risk factors for sleep-disordered breathing. For a group that is young (mean age, <30 years), healthy, and physically fit, this is a worrisome finding. The presence of sleep-disordered breathing (apnea-hypopnea index,  $\geq 5$ ), even in persons without symptoms, is a known risk factor for the development of hypertension.<sup>5</sup> Treatment of sleep-disordered breathing will presumably reduce the risk of cardiovascular disease, but its presence must first be recognized.

As the trend toward bigger football players continues, unrecognized and untreated sleep-disordered breathing may affect not only the players' performance and productivity but also their future health. Many physicians may have never considered such a diagnosis in young, healthy persons, particularly those who are in top condition. Clinical sus-

**Table 1. Prevalence of Sleep-Disordered Breathing in Professional Football Players.\***

Apnea-Hypopnea Index	High Risk (N=38)		Low Risk (N=14)		Weighted Sample†
	No.	Rate (95% CI)	No.	Rate (95% CI)	Rate (95% CI)
<5.0	16	0.42 (0.28-0.58)	12	0.86 (0.60-0.96)	0.75 (0.38-1.0)
5.0-9.9	9	0.24 (0.13-0.39)	1	0.07 (0.01-0.31)	0.11 (0.01-0.22)
$\geq 10.0$	13	0.34 (0.21-0.50)	1	0.07 (0.01-0.31)	0.14 (0.02-0.25)

\* The group was divided into players with a high risk or a low risk of sleep-disordered breathing, according to the multivariable apnea-prediction index (in which scores range from 0 to 1, with higher scores indicating a greater risk of sleep-disordered breathing). A score of  $\geq 0.5$  was considered to indicate a high risk and a score of <0.5 a low risk. CI denotes adjusted Wald confidence interval.

† Weighted-sample rates are population-standardized rates.

picion should now be raised in these and other athletes as well as members of the general population who are of similar age and size.

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## Driving Fatalities on Super Bowl Sunday

**TO THE EDITOR:** The Super Bowl is the most popular regular television broadcast in the United States, with an audience of about 130 million Americans. We studied driving fatalities on 27 consecutive Super Bowl Sundays, because alcohol, inattention, and fatigue are major contributors to fatal motor vehicle crashes.<sup>1</sup> To do so, we compared each Super Bowl Sunday to the immediately preceding and subsequent Sundays (comparisons that controlled for season of the year, day of the week, and calendar year).

The time from kickoff to the end of the game defined three time intervals—namely, before, during, and after the telecast.<sup>2</sup> The same times were used for corresponding control Sundays (to ensure identical intervals in relevant comparisons), and values were converted to Greenwich mean time (to account for varying time zones of telecasts and crashes). Population-based data on fatal motor vehicle crashes were obtained from the Fatality Analysis Reporting System<sup>3</sup> for all available years (1975 to 2001).

We observed a 41 percent relative increase in the average number of fatalities after the telecast (24.5 vs. 17.3,  $P < 0.001$ ). In contrast, we observed no significant difference between Super Bowl Sundays and control Sundays in fatalities before the telecast (68.9 vs. 67.0,  $P > 0.20$ ) and a marginal decrease during the telecast (15.7 vs. 17.7,  $P = 0.036$ ). The increase in fatalities after the telecast was evident for 21 of 27 years and amounted to about seven added deaths on the average Super Bowl Sunday as compared with the average control Sunday.

The increase in fatalities after the telecast also applied to nonfatal injuries (Fig. 1, facing page

and was generally larger in states with a losing team than neutral states and larger in neutral states than states with a winning team (68 percent vs. 46 percent vs. 6 percent,  $P = 0.003$ ). New York and Colorado had the most losses (five and four, respectively) and showed a 147 percent increase for the nine relevant years (95 percent confidence interval, 1 to 510). California had the most wins (eight) and showed no evidence of an increase (change,  $-4$  percent; 95 percent confidence interval,  $-24$  to 22) during those eight years.

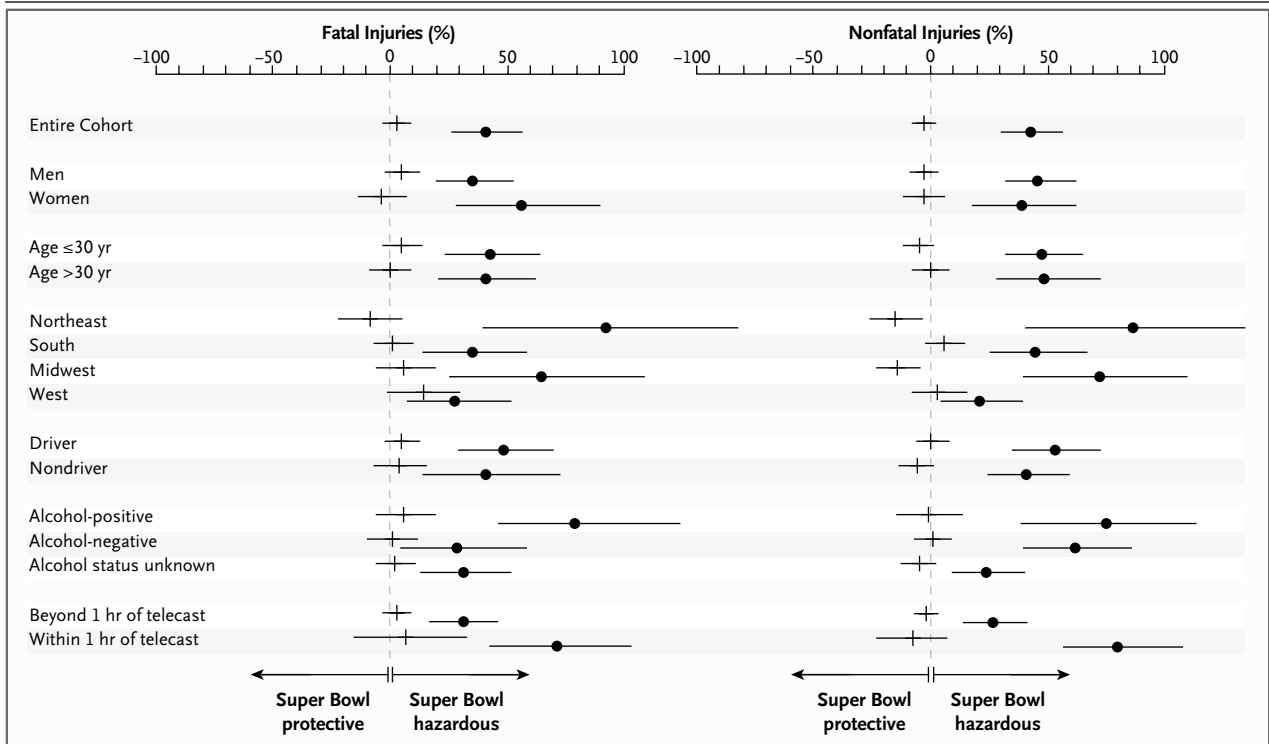
The 41 percent relative increase in fatalities after the Super Bowl telecast exceeds the relative increase in fatalities on New Year's Eve that has prevailed for the past two decades in the United States.<sup>4</sup> Hence, one option could be for sponsors to support subsidized public transit after the telecast. In the interim, clinicians in trauma centers might consider extra staffing, and clinicians in ambulatory care offices might warn patients to avoid unnecessary night driving on Super Bowl Sunday.

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**Figure 1. Relative Increase in the Risk of Fatal Injuries and Nonfatal Injuries on Super Bowl Sundays, as Determined from Observed Counts, Shown as Percentages and 95 Percent Confidence Intervals.**

Time after the telecast is indicated by solid circles, and time before the telecast by vertical bars. The dashed vertical line indicates no relative increase in risk on Super Bowl Sundays as compared with control Sundays. The primary analysis of the entire cohort of persons with fatal injuries showed no significant increase in the risk of death during the hours before the telecast and a 41 percent increase in the risk of death during the hours after the telecast. Similar patterns were evident in separate analyses of nonfatal injuries, and zero was excluded from all confidence intervals for the hours after the telecast. Taking into account the similarity in risk before the time of the telecast and the decrease in risk during the time of the telecast, the net increase in risk of 41 percent in the primary analysis contributes to an absolute increase of 189 deaths over the entire day for the 27 Super Bowl Sundays.

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