

## Correspondence



## Implantable Cardiac Defibrillators

*To the Editor:* Moss et al. (March 21 issue)<sup>1</sup> describe a randomized, controlled clinical trial designed to test the expansion of the indications for implanting a cardiac defibrillator. The maker of the defibrillator paid for the trial, which was conducted by experts in the procedure that uses the defibrillator. The results demonstrate an unquestionable 31 percent decrease in mortality among those who underwent the prophylactic procedure. The accompanying editorial by Bigger<sup>2</sup> cites the need for additional data and longer follow-up and implies that expanding the indications for the procedure may be premature. Nevertheless, nationally prominent cardiologists perceive the results of the trial as clearly demonstrating the efficacy of expanded use of the procedure.<sup>3</sup>

If Blue Cross or Medicare had sponsored the same trial and if experts in clinical epidemiology had directed the research, would the investigators have used the same results to recommend wider application of the procedure? Would they have failed to describe an absolute survival benefit of only 5.6 percent, to specify the cost of the procedure, to estimate the cost per life saved, or to recommend longer follow-up before drawing conclusions? Would their article have received a high priority for publication, been accompanied by a two-page advertisement for its sponsor, or attracted widespread media attention? Even when investigators without financial conflicts of interest have conducted a clinical trial carefully, we still need to pay attention to who pays for and who performs the trial as we consider what the published results mean.

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2. Bigger JT. Expanding indications for implantable cardiac defibrillators. *N Engl J Med* 2002;346:931-3.
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*To the Editor:* If one assumes a conservative one-time cost of \$30,000 per cardiac-defibrillator implantation (range, \$28,000<sup>1</sup> to \$57,700<sup>2</sup>), heeding the call of Moss et al. to provide an implantable cardiac defibrillator for the estimated yearly flow of 400,000 new patients would cost public and private payers \$12 billion annually. This cost alone is three times the estimated 2003 budget for the Centers for Disease Control and Prevention.<sup>3</sup> If the additional government spending required to cover these devices were contemplated in other contexts, it would rightly be debated as a costly new program that competes with others for scarce public funds. Yet as part of a health care entitlement, implantable cardiac defibrillators highlight the surprisingly limited opportunities for policymakers and the public to shape the development and use of new forms of technology. When they have been proved to be safe and effective, lifesaving treatments bring strong political and clinical claims for reimbursement, regardless of the broader implications.

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## INSTRUCTIONS FOR LETTERS TO THE EDITOR

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*To the Editor:* Several issues should be addressed regarding therapy with an implantable defibrillator before widespread consideration of this treatment is recommended. The study by Moss et al. was not blinded. Patients were randomly assigned to receive a defibrillator or not to receive a defibrillator. Since the device is noticeable during examination, unrecognized bias may have been introduced in the form of preferential treatment for patients who received defibrillators. This potential bias could have been minimized if all enrolled patients had received a defibrillator and then been randomly assigned to activation or nonactivation of the device.

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*To the Editor:* Moss et al. report that the survival of patients with a reduced ejection fraction after myocardial infarction improved with the implantation of a defibrillator. The defibrillator group was compared with patients receiving conventional therapy alone. Table 1 of the report shows very few differences between the defibrillator group and the conventional-therapy group in terms of their medical regimens; however, there is no mention in the table or the text of the article of the use of aspirin, anticoagulants, or other antiplatelet agents in either group. Given that prolonged aspirin therapy in high-risk patients has been shown to reduce the rate of death from vascular causes and to improve overall survival,<sup>1</sup> could the survival difference between the two groups in the study by Moss et al. be attributable to a difference in their use of aspirin or other antiplatelet therapies?

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1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106. [Erratum, *BMJ* 1994;308:1540.]

*To the Editor:* We could wait for the future analysis, mentioned by Bigger, of the results of electrophysiological testing performed during implantation of the defibrillator. But data regarding the effect on survival of the rates of defibrillator discharge are crucial for the interpretation of the results of the study by Moss et al. and should therefore have been included in their article.

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*To the Editor:* The fundamental issue is whether death due to ventricular tachycardia or ventricular fibrillation can be averted by implantation of a defibrillator in patients with

severe ischemic cardiomyopathy. The clinical decision is whether to use drug therapy (amiodarone or sotalol) or a defibrillator. It is odd that Moss et al. did not compare defibrillator treatment with amiodarone or sotalol. The inevitable question is whether the defibrillator is superior to class III drugs — not whether it is superior to no antiarrhythmic therapy at all. Since no attempt was made to resolve this issue, the study leaves us in the same quandary in which we began.

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The authors reply:

*To the Editor:* We fully agree with Drs. Carbajal and Smith that blinded studies are less subject to bias than unblinded ones. However, the use of sham implantations would not have been ethical or feasible, nor would it have resulted in a truly blinded study. Given that scheduled office visits to cardiologists were made almost equally often in both groups, with attendance rates above 90 percent, it is difficult to imagine that there could have been a treatment bias sufficient to cause a 31 percent decrease in the risk of death from any cause.

As Dr. Donaldson argues, it is reasonable when evaluating recommendations based on a study to take into consideration who paid for the study and who conducted it, but the study results themselves clearly stand. We would all like to know what the longer-term results will be, but we disagree that an absolute reduction in mortality of 5.6 percent (from 19.8 percent to 14.2 percent) with defibrillator therapy over an average follow-up period of 20 months is a small effect or one that would ethically preclude continued experimentation in patients. Should we withhold medical results because society, whether pressured by cardiologists or by the politics of health care delivery, may misuse them?

Like Drs. Stecker and Pollack and Dr. Donaldson, we are fully aware of the potential cost and reimbursement implications of our study and other studies of defibrillators.<sup>1,2</sup> An evaluation of the cost effectiveness of treatment with an implantable cardiac defibrillator in our study is under way. Clinical trials designed to determine whether a specific type of therapy saves lives represent a first step in advancing the science of medical therapeutics. Only when therapy is shown to be scientifically efficacious should cost considerations come into play. We do not believe that policymakers should shape the development and use of new forms of technology before their therapeutic efficacy has been demonstrated — that would be putting the cart before the horse.

Regarding Dr. Cohen's concern, aspirin was used by 63 percent and 65 percent of patients in the defibrillator and conventional-therapy groups, respectively. The rate of discharge of the defibrillators is a relevant question raised by Dr. Gollapudi, and preliminary data indicate that defibrillator therapy for malignant ventricular arrhythmias accounts for the reduction in mortality. Complete analyses will appear in due course. The executive committee for the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) decided not to use amiodarone or sotalol for comparison

in the trial, as Dr. Spivak suggests, since the evidence that was available before the trial began indicated that class III drugs had no benefit and might cause harm in patients who had had a myocardial infarction.<sup>3,4</sup>

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### Comparison of Angioplasty with Stenting in Acute Myocardial Infarction

*To the Editor:* The results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study, reported by Stone et al. (March 28 issue),<sup>1</sup> convincingly validate primary stent implantation as a preferred strategy for the treatment of acute myocardial infarction. However, despite a similar incidence of the primary composite end point (death from any cause, reinfarction, revascularization, or disabling stroke) at six months between patients who received stents with abciximab (10.2 percent) and those who received stents without abciximab (11.5 percent), the study should not be misconstrued as demonstrating that the administration of abciximab during primary stenting is of no benefit. Previous randomized, double-blind studies<sup>2,3</sup> have demonstrated approximately a 50 percent reduction in adverse cardiovascular events with abciximab in this setting.

In the CADILLAC trial, the comparison of stenting alone with stenting plus abciximab was not a prespecified hypothesis. Furthermore, the inclusion of patients who had myocardial infarction without ST-segment elevation (12 percent), combined with the exclusion of patients at high risk (those with prior bypass surgery, shock, or lesions not suitable for stenting) resulted in the selection of patients at lower risk than those previously studied. For instance, in the CADILLAC study, 30-day mortality in the group of patients who underwent stenting without receiving abciximab was 2.2 percent, as compared with 4.5 percent in the Intracoronary Stenting and Antithrombotic Regimen 2 (ISAR-2) study,<sup>2</sup> 6.6 percent in the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up study (ADMIRAL),<sup>3</sup> and 5.8 percent in a recent, large trial of fibrinolysis.<sup>4</sup> The 4.7

percent of patients in the stenting-alone group who received abciximab in the CADILLAC study, which was unblinded, also confounds the analysis of this issue. Although the findings suggest that low-risk patients who are pretreated with a thienopyridine had relatively little benefit from abciximab therapy, the weight of prior evidence from nonrandomized and randomized studies of percutaneous coronary intervention, as well as studies of such interventions as rescue treatment, supports the routine use of abciximab in patients with acute myocardial infarction.

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*Editor's note:* Dr. Herrmann has received research support and honorariums from companies that manufacture pharmaceutical agents that are relevant to this study, including but not limited to Lilly Research Laboratories, a sponsor of the study.

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The authors reply:

*To the Editor:* We thank Dr. Herrmann for his thought-provoking comments. Although the CADILLAC study clearly supports routine stent implantation in patients with acute myocardial infarction, the clinical implications for routine use of abciximab are less certain. Both the ADMIRAL<sup>1</sup> and ISAR-2<sup>2,3</sup> studies were modest in size, and neither trial used loading with a thienopyridine, which is the current standard of care. ISAR-2 allowed prior lytic therapy and enrollment up to 48 hours after the onset of symptoms, and the ADMIRAL study evaluated early administration of abciximab, before angiography. Indeed, the benefits of abciximab in the ADMIRAL study were confined to patients who received the drug in the ambulance or emergency room; this group had a 90 percent reduction in events,<sup>2</sup> which is well out of proportion to real-world expectations. Moreover, contrary to Dr. Herrmann's comments, in the CADILLAC study, the cohort of patients without ST-segment elevation was a high-risk population (as shown in Fig. 1 of our article), and analysis according to the treatment actually received showed that the rate of adverse events at six months was 10.4 percent among patients who underwent stenting with abciximab, as compared with 10.9 percent among those who underwent stenting without abciximab (P=0.61).

The results of the CADILLAC study are representative of the outcomes that can be expected with current techniques

and adjunct pharmacotherapy. We reiterate our conclusions that abciximab, given just before intervention, reduces early recurrent ischemia and subacute thrombosis and facilitates earlier discharge (by approximately 0.5 day), though long-term benefits may not accrue in terms of late clinical events, restenosis, or myocardial recovery. With the principal caveats that patients with shock were excluded and that the trial was statistically underpowered for an assessment of mortality, each physician will need to interpret the relevance of these data to his or her own practice.

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*Editor's note:* Drs. Stone, Grines, and Tcheng have received research support from or have served as consultants to companies that manufacture interventional devices or pharmaceutical agents relevant to this study, including but not limited to Guidant and Lilly Research Laboratories, two of the sponsors of the study.

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### Amiodarone versus Lidocaine for Shock-Resistant Ventricular Fibrillation

*To the Editor:* Dorian and colleagues (March 21 issue)<sup>1</sup> report increased rates of survival to hospital admission among patients treated with amiodarone for out-of-hospital ventricular fibrillation. Although their conclusion is consistent with their data and is in accordance with those reported previously by Kudenchuk and coworkers,<sup>2</sup> the questions of cost versus benefit and of reasonable outcome measures are raised. The results presented by Dorian et al. suggest that treatment of 100 patients could result in 10 additional hospital admissions but survival to discharge from the hospital for only 1 additional patient, without proven neurologic recovery.

In both studies, the use of amiodarone was associated with an increase in the percentage of admitted patients who died or who had adverse neurologic outcomes: the increase was 8.8 percentage points (32 of 180 patients treated with amio-

darone vs. 15 of 167 treated with lidocaine) in the current study<sup>1</sup> and 9.2 percentage points (75 of 246 patients who received amiodarone vs. 55 of 258 who received placebo, respectively) in the study by Kudenchuk et al.<sup>2</sup> Kudenchuk et al. reported that the rate of survival with good neurologic recovery with amiodarone was similar to that without amiodarone (7.3 percent vs. 6.5 percent). If this difference were significant, the number needed to treat would be 125. If all the discharged patients in the study by Dorian et al. had good neurologic outcomes, the combined data would yield an absolute reduction in the rate of death or an unfavorable neurologic outcome of 1.0 percent (5.3 percent with amiodarone vs. 6.3 percent with lidocaine or placebo). Since approximately 650,000 out-of-hospital cardiac arrests occur in the United States<sup>3</sup> and Europe<sup>4</sup> annually, with 10 percent meeting the inclusion criteria of these two studies,<sup>1,2</sup> the use of amiodarone in 65,000 patients would result in an additional 650 patients surviving to discharge from the hospital, at the price of 5850 additional nonsurvivors.

In the light of considerable suffering, limited intensive-care-unit resources, and additional hospital costs, we agree that the use of amiodarone in persons who have an out-of-hospital cardiac arrest should be thoroughly investigated. We hope that the use of mild therapeutic hypothermia (with a combined number needed to treat of six for survival with a good neurologic outcome, without increased in-hospital mortality, in two recent studies<sup>4,5</sup>) will also benefit patients resuscitated with the use of amiodarone.

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*To the Editor:* Although an increase in the rate of survival to admission is a laudable intermediate outcome, there are many potential harms if the rate of survival to discharge is not also improved. In the study by Dorian and colleagues, because there was no improvement in long-term survival, the 90 percent relative improvement in survival to hospitalization substantially increased costs and prolonged the suffering of patients and families, without any long-term benefit. Can the authors provide information on the length and costs of hospitalization among short-term survivors?

On average, 24 minutes elapsed from the time of dispatch to the time of administration of the study drug. With an

interval this long, even though amiodarone improves the restoration of spontaneous circulation, there is frequently permanent neurologic damage as a result of prolonged hypoxia, making the potential for an improvement in long-term survival remote. The authors did find that the rate of short-term survival was higher among patients treated less than 24 minutes after the time of dispatch than in those treated after 24 minutes. We would be interested to know whether there was a trend toward improved long-term survival in the patients who were treated after the shorter interval. If so, future studies could focus on the use of amiodarone in such patients; these studies should be designed to demonstrate improvement in both short-term and long-term rates of survival.

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*To the Editor:* Dorian et al. believe that their research proves that amiodarone is the drug of choice for shock-resistant ventricular fibrillation. The focus of their research is patients who survive to hospital admission. However, only nine of the patients in the amiodarone-treated group survived to discharge, as compared with five of those in the lidocaine-treated group. Two extremely important questions are not addressed by their article. First, what was the neurologic outcome in the survivors? If the patients were discharged alive but without clinically significant neurologic recovery, then I believe the outcome would be worse for society than the patients' deaths. Second, if the total number of patients discharged without neurologic deficits was no higher with amiodarone than with lidocaine, then surely the survival of many more patients to hospital admission, with the subsequent costly yet futile hospital stay, is once again a bad outcome for society as a whole.

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*To the Editor:* We are concerned about the use of polysorbate 80 in the lidocaine group in the study by Dorian et al. Polysorbate 80 (the diluent of intravenous amiodarone) is considered to have hypotensive effects and to cause a decrease in the heart rate and atrioventricular conduction disturbances.<sup>1,2</sup> All the patients in the lidocaine group received lidocaine combined with polysorbate 80 as a so-called matching placebo. This cannot be considered an inactive placebo. The mixture of polysorbate 80 and lidocaine was used in order to have identical-looking drug containers, as part of the double-blind study design (Dorian P: personal communication). This design followed that of the Amiodarone in Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia study, in which amiodarone was compared with polysorbate 80 (as placebo)<sup>3</sup> and the results of

which contributed to the recommended use of amiodarone in the guidelines for advanced cardiac life support.<sup>4</sup>

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The authors reply:

*To the Editor:* Silfvast and Pettilä, Ballew and Philbrick, and Tomkiewicz all comment on the important question of the benefits versus the cost of attempting to resuscitate patients after out-of-hospital cardiac arrest. The design of our study does not permit definitive conclusions about the potential for treatment with intravenous amiodarone to improve long-term outcomes in patients resuscitated after shock-resistant ventricular fibrillation. However, the in-hospital rates of death in the amiodarone and lidocaine groups in our study were 78 percent and 75 percent, respectively — similar to in-hospital death rates reported previously.<sup>1</sup> In our study, 64 percent of the patients discharged alive had a favorable neurologic outcome (a Glasgow-Pittsburgh Scale score of at least 4 on a scale from 1 to 5, where higher scores indicate a better outcome). The number of survivors who were treated early (less than 24 minutes after dispatch) as compared with late (24 minutes or more after dispatch) was too small to allow meaningful conclusions about the effect the time to treatment had on rates of discharge from the hospital. We agree with Ballew and Philbrick that it is reasonable to suppose that earlier treatment, and thus earlier restoration of effective circulation, may be expected to result in better ultimate neurologic outcomes and believe that this should be investigated in future clinical trials. With respect to overall costs and effectiveness of advanced care before hospital admission, it is important to remember that other commonly used therapies, such as intravenous epinephrine or defibrillation with automated devices by first responders, have not been shown in randomized trials to improve survival to hospital discharge.<sup>2</sup>

With respect to our use of polysorbate 80 in the lidocaine-treated group, since the diluent used in the preparation of amiodarone foams and is highly viscous, it would not have been possible to blind the study adequately by using some other compound (e.g., 5 percent dextrose in water). In addition, bolus administration of the diluent alone results in transient increases in the heart rate and decreases in blood pressure lasting four minutes but does not result in a signif-

icant decrease in indexes of contractility.<sup>3</sup> A comparison of the effects of amiodarone with polysorbate 80 as a diluent and without it showed similar results. It is thus unlikely that the diluent was responsible for the observed differences between the amiodarone and lidocaine groups.<sup>4</sup>

Finally, as Silfvast and Pettilä point out, one can hope that the sequential administration of therapies that may be effective in early resuscitation and improved subsequent care of patients who have had a cardiac arrest will result in measurable and useful improvements in long-term survival.<sup>1,2</sup> Much research needs to be done to optimize advanced cardiac life support.

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## Fluconazole for the Treatment of Cutaneous Leishmaniasis

*To the Editor:* Alrajhi et al. (March 21 issue)<sup>1</sup> report on the efficacy of systemic fluconazole for Old World cutaneous leishmaniasis caused by *Leishmania major*. Although this therapy was more efficacious than placebo, the rationale for the study is questionable. Because of potential side effects and high costs, it is unlikely that any systemic therapy will ever become the first-choice therapy for uncomplicated Old World cutaneous leishmaniasis, which is a self-limited skin disease that is usually amenable to topical treatments. Moreover, the cost of six weeks of treatment with fluconazole at a dose of 200 mg per day is about \$550. It would be more useful to evaluate the efficacy of fluconazole in patients with no response to topical therapy.

Currently, ointment containing 15 percent paromomycin (Leshcutan, Teva Pharmaceutical) is the treatment of choice for Old World cutaneous leishmaniasis in Israel (where *L. major* is also the most common pathogen). This treatment results in a cure rate of 76 to 86 percent after a single two-week course of daily topical application.<sup>2,3</sup> Promising

results have also been reported with topical amphotericin B therapy.<sup>4</sup>

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The authors reply:

*To the Editor:* We agree with Zvulunov et al. that an efficacious, well-tolerated topical agent for the treatment of cutaneous leishmaniasis is highly desirable, particularly for persons with small numbers of lesions on parts of the body other than the face. Although el-On et al.<sup>1</sup> reported successful treatment of lesions caused by *L. major* with topical paromomycin, randomized trials in four different countries demonstrated that the efficacy of this treatment was poor.<sup>2-5</sup> Topical paromomycin is currently not available in Saudi Arabia. We do not agree that adverse effects of systemic fluconazole, which were minimal in our study and in other studies, should discourage the evaluation of new indications for its use, including cutaneous leishmaniasis due to *L. major* outside of Saudi Arabia. The cost of fluconazole is high, but there may be a drop in the price in the near future, particularly when the patent on the drug expires.

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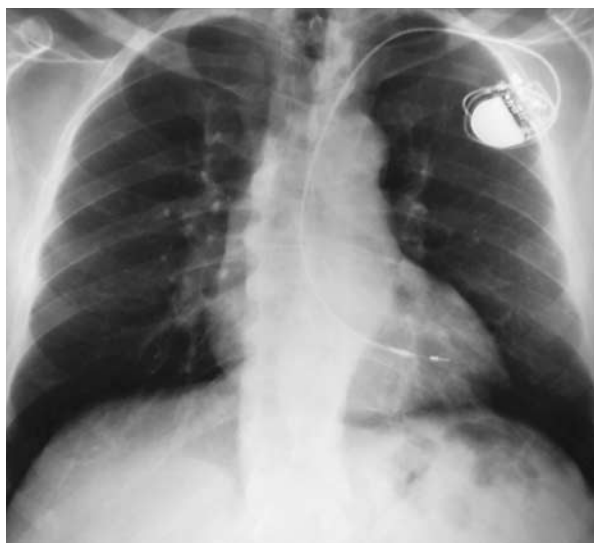
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### Medical Mystery — The Answer

*To the Editor:* The medical mystery in the June 13 issue<sup>1</sup> involved a 76-year-old man with sinus node disease who was evaluated after an episode of syncope and who received a single-chamber pacemaker through the left subclavian ap-



**Figure 1.** Medial Pathway of the Pacing Lead. The lead enters the subclavian artery, crosses the aortic valve, and comes to rest in the left ventricle.

proach. The medial pathway of the pacing lead on the chest film (Fig. 1), coupled with the finding of right bundle-branch block on the paced electrocardiogram (Fig. 2), confirms that the lead had been passed by means of the subclavian artery through the ascending aorta, across the aortic valve, and into the left ventricle. A new, dual-chamber pacemaker was placed through the right side of the chest, and once stable pacing had been established, the left-sided pacemaker pocket was opened, the generator was removed, and the lead was retracted to the level of the subclavian artery but temporarily left in place to avoid arterial bleeding. The residual fragment of the lead was then removed by a vascular surgeon, who repaired a laceration of the inferior margin of the subclavian artery caused by the original procedure.

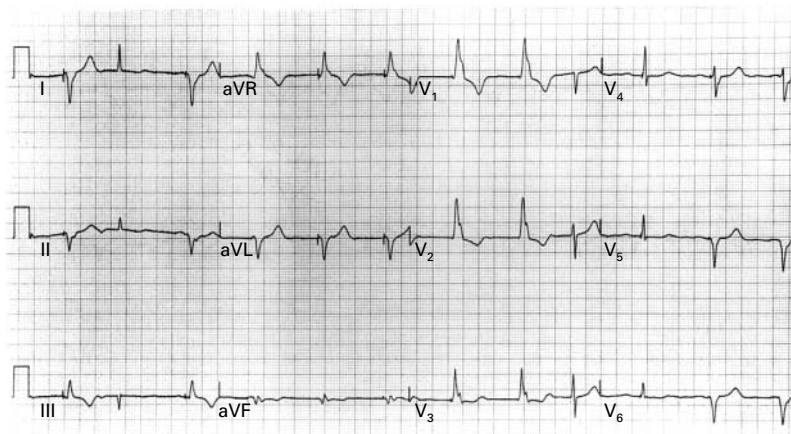
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*Editor's note:* We received 258 responses to this medical mystery; 79 percent of responses indicated that the pacemaker lead had erroneously been placed into the left ventricle. Other responses included insertion of the pacemaker into the coronary sinus (7 percent), perforation of the interventricular septum by the lead (3 percent), and insertion of the lead into the right ventricle (2 percent).

### A Controlled Trial of Geriatric Evaluation

*To the Editor:* On the basis of a trial that showed little effect of geriatric evaluation and management, Cohen et al. (March 21 issue)<sup>1</sup> conclude that earlier studies might have overestimated the benefits of this type of geriatric care.<sup>2</sup> This conclusion is premature. The blinding of geriatric teams meant that inpatient care and outpatient care were artificial-



**Figure 2.** Electrocardiogram Showing Right Bundle-Branch Block.

ly separated, rather than integrated. The outpatient component was of low intensity and could have consisted of a single follow-up visit. The population was selected on the grounds of frailty, rather than on the basis of the presence of modifiable risk factors, and most of the patients were men. Finally, the validity of the Medical Outcomes Study 36-item Short-Form General Health Survey questionnaire for assessing the functional status in frail elderly people is questionable.<sup>3</sup>

The results of the study by Cohen et al. should not be interpreted as invalidating the results of previous trials that demonstrated substantial benefits of geriatric assessment.<sup>4</sup> Geriatric assessment programs are complex, multifaceted interventions that have been implemented differently in different settings. Heterogeneous results are to be expected. The challenge is to determine which components of the intervention are effective and what populations are most likely to benefit. A recent analysis of trials of home visits that aim to prevent functional decline indicates that programs with multidimensional assessments and follow-up do work, particularly if they are offered to older persons with relatively good function at base line.<sup>5</sup> A similar analysis of the trials of geriatric evaluation and management is now required.

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*To the Editor:* The discouraging findings reported by Cohen et al. set the stage for a debate concerning the interpretation of the results and their implications for future geriatric programs. Over the course of the nearly 20 years since the introduction of the principles of geriatric evaluation and management,<sup>1</sup> usual care may have become more and more like the programs of geriatric evaluation and management described in earlier studies. In the Veterans Affairs system, there have been many formal interventions to improve the quality of care, and the hospitals participating in the trial

were selected because of established programs and a record of good geriatric care.

Such general improvement could indicate that the geriatrics mission has been accomplished, at least in these Veterans Affairs hospitals. However, efficacy of the geriatric evaluation and management approach as compared with that of internal medicine or other medical specialties remains untested.<sup>2</sup> There are reports of continued and consistent advantages for patients who receive care through programs of geriatric evaluation and management.<sup>3,4</sup> On the basis of a recent analysis, home-based programs for the elderly appear to reduce the rates of functional decline, nursing home admissions, and mortality.<sup>5</sup>

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*To the Editor:* The results of the trial by Cohen et al. must be interpreted with caution. Only 3 percent of all screened patients were enrolled in the study, 98 percent of them were men, and the mean age was 74.2 years. In our similarly designed study with 545 participants, the mean age was 81.4 years, and 73.4 percent of our patients were women. The functional status of study participants was similar in the two trials, but in our study the interventions were more effective.<sup>1</sup> A subgroup of our patients with severe functional impairment (Barthel score,  $\leq 65$  points) benefited most in terms of prevention of rehospitalization or nursing home placement. Compliance with treatment recommendations was a crucial issue with respect to the effectiveness of our intervention. The rate of compliance was higher among women than among men ( $P=0.04$ ). Although the incidence of disability seems to be similar among men and women,<sup>2</sup> the effects of an intervention are not necessarily the same.

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*To the Editor:* In the study by Cohen et al., 3 percent of screened patients chose to enroll and 4 percent refused to enroll or did not have a telephone. Perhaps the authors could comment on whether volunteer bias could have affected their results. The eligible patients who declined enrollment presumably were aware that refusal of consent would result in a greater likelihood of admission to the inpatient unit for geriatric evaluation and management than the 50 percent chance provided by this randomized trial.

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The authors reply:

*To the Editor:* In response to the remarks of Stuck et al. regarding our conclusions, the greatest difference between our trial and previous trials in geriatric evaluation and management units was in the effects on survival. We concluded that although methodologic issues may have been involved, it is also possible that usual care has evolved (as Bernabei et al. suggest) so that the difference between such care and that provided by geriatric evaluation and management programs has been reduced. The mortality rate of 20 percent with usual care was considerably lower than that in the earlier studies.<sup>1,2</sup> We believe that geriatric evaluation and management units provide a substantial benefit in reducing in-hospital functional decline and that the magnitude of the effect of outpatient geriatric evaluation and management is similar to that of the effects seen in most previous studies.<sup>2</sup> Although blinding may have affected planning before discharge, there was ample communication between the inpatient and outpatient teams (whose staff often overlapped), so it is unlikely that blinding would have had much of an effect in the long term. There is no reason to suspect that the outpatient programs were of lower intensity than other programs. Patients in all groups averaged between one and two outpatient visits per month. Frailty has been the basis for the selection of patients in most previous studies of geriatric evaluation and management, and we targeted patients with the use of similar generally accepted criteria. We agree with Stuck et al. as well as Bernabei et al. that there may be other types of programs that might be effective and other target groups and outcomes that might be affected. We hope that they will be evaluated in rigorous trials in the future.

The study that Drs. Nikolaus and Becker describe tested a different intervention<sup>3</sup> — direct admission to a geriatric center for assessment, in combination with in-home intervention. Their trial demonstrated efficacy in reducing the length of stay in the hospital and the rate of immediate placement in a nursing home. However, as in our trial, there was no difference in survival, and no difference in overall functional status, although the number of activities of daily living for which they were dependent on others was reduced. Their patients also had higher self-ratings of health. As we noted, theirs is an approach worthy of further study.

As Dr. Meuleman suggests, volunteer bias can affect any clinical trial, but there was no indication that a desire to ensure admission to the unit had an influence. If anything, patients more often refused because they did not want to risk having to remain in the hospital longer.

Current programs of geriatric evaluation and management should not have to justify themselves on the basis of a survival advantage. For frail elderly persons, maintenance of the quality of life and functional status are at least as important, and such programs do appear to improve function.

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### Use of a Proton-Pump Inhibitor for Metabolic Disturbances Associated with Anorexia Nervosa

*To the Editor:* Eiro et al. (Jan. 10 issue)<sup>1</sup> report that therapy with a proton-pump inhibitor may be useful in correcting the metabolic abnormalities in patients with eating disorders involving self-induced vomiting. Although the loss of hydrogen ions initiates vomiting-induced metabolic alkalosis, the primary reason that the alkalosis persists is the loss of sodium chloride. The resultant reduction in intravascular volume leads to an increase in aldosterone secretion, which increases sodium bicarbonate reabsorption by the distal nephron and results in maintenance of the metabolic alkalosis. Proton-pump inhibitors do not affect this primary causal factor.

As a corollary, the efficacy of potassium repletion is abrogated in patients with volume depletion and hypokalemia, unless there is concomitant normalization of the hypovolemic state.<sup>2</sup> Once volume depletion has been corrected, there is down-regulation of aldosterone secretion. Only then will potassium repletion be successful.<sup>3</sup> Proton-pump inhibitors alone would therefore not be expected to reverse hypokalemia caused by self-induced vomiting.

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The authors reply:

*To the Editor:* We completely agree with Drs. Mehler and Linas that a principal problem in patients with self-induced vomiting is dehydration leading to secondary aldosteronism. Volume replacement is the first-line therapy for such patients. However, intermittent volume-replacement therapy is not routinely feasible in patients with bulimia, who may be reluctant to accept intravenous infusion of fluids; moreover, these therapies generally require that the patient come to the hospital.

With vomiting, chloride is secreted in gastric fluid as hydrogen chloride, and sodium and potassium are excreted in urine along with an unreabsorbed anion, bicarbonate, causing an increase in the urinary anion gap. Thus, as long as self-induced vomiting continues, these disturbances persist. In the patient we described, a proton-pump inhibitor reduced hydrogen chloride secretion in the stomach and minimized the loss of these electrolytes into the vomitus. Secondly, there was less urinary excretion of bicarbonate and associated cations, which was reflected in a decreased urinary anion gap. As Drs. Mehler and Linas note, correction of dehydration and sufficient supplementation of electrolytes is indispensable, and treatment of the underlying disorder should be a central focus.

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### Treatment of High-Grade Vaginal Intraepithelial Neoplasia with Imiquimod Cream

*To the Editor:* Primary invasive carcinoma of the vagina is rare, accounting for less than 3 percent of malignant tumors of the female genital tract. Vaginal intraepithelial neoplasia, a precursor of invasive vaginal carcinoma, is even less common.<sup>1</sup> Cytologic screening for vaginal tumors is not useful, unless there is a history of neoplasia of the lower genital tract.<sup>2,3</sup> We treated three women with high-grade vaginal intraepithelial neoplasia by applying 5 percent imiquimod cream vaginally. Imiquimod induces the secretion of interferon- $\alpha$ , interleukin-12, and tumor necrosis factor  $\alpha$  from mononuclear cells.

All three women were positive for the high-risk type of human papillomavirus before treatment. The treatment consisted of vaginal application of 5 percent imiquimod cream

under colposcopic guidance three times a week for eight weeks. The first patient was a 38-year-old woman who had grade 3 vaginal intraepithelial neoplasia after undergoing a hysterectomy for cervical intraepithelial neoplasia, grade 3. Biopsy specimens obtained after treatment with imiquimod showed grade 1 vaginal intraepithelial neoplasia. The second patient was a 61-year-old woman who had multifocal lesions of grade 2 vaginal intraepithelial neoplasia after undergoing a hysterectomy for leiomyomas. Histologic studies performed after therapy revealed human papillomavirus infection without any indication of vaginal intraepithelial neoplasia. The third patient was a 58-year-old woman who had grade 3 vaginal intraepithelial neoplasia after undergoing a hysterectomy for microinvasive carcinoma of the cervix. Follow-up histologic studies showed regression to grade 1 vaginal intraepithelial neoplasia. There were no adverse events related to the use of the cream. Before the application of imiquimod, the p53 protein was overexpressed in biopsy specimens from the first and third patients, but not in specimens from the second. After treatment, histologic studies showed no p53-positive nuclei in the first and second patients, whereas the third continued to have overexpression of the protein.

Imiquimod is a locally active immune-response modifier that stimulates natural-killer-cell activity, enhances functional maturation of Langerhans' cells, and augments the effectiveness of T cells.<sup>4</sup> Davis et al. recently reported that imiquimod therapy produced good results in four women who had high-grade vulvar intraepithelial lesions (vulvar intraepithelial neoplasia, grade 3).<sup>5</sup> In our patients, application of the cream under colposcopic guidance ensured the spread of the drug into the folds, rugae, and angular funnels of the vagina. Histologic studies performed after treatment revealed regression of the disease by at least two grades. Our findings suggest the imiquimod is an alternative conservative therapy for vaginal intraepithelial neoplasia.

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