

# High Impact of Antiphospholipid Syndrome on Irreversible Organ Damage and Survival of Patients With Systemic Lupus Erythematosus

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**Background:** Thrombosis is a frequent cause of morbidity and death in patients with systemic lupus erythematosus (SLE). Whether antiphospholipid syndrome (APS) is the cause of increased irreversible organ damage and mortality in lupus patients is not well established.

**Methods:** Prospective inception cohort of 202 patients with SLE (American College of Rheumatology criteria). Antiphospholipid syndrome was defined according to the Sapporo criteria. Irreversible damage was measured using the Systemic Lupus International Collaborating Clinics–American College of Rheumatology damage index (SDI) at 6 months and 1, 3, 5, 10, 15, 20, and 25 years after the diagnosis of SLE. All deaths were documented.

**Results:** A total of 88% of patients were women. Twenty-

eight patients met criteria for definite APS. Mean (SD) follow-up was 9.7 (6.0) years. Nine patients could not be contacted for follow-up. All patients with APS experienced thrombosis, most of them in the arterial bed. Damage was more severe in patients with APS than in those without APS (median SDI score, 2 vs 0 at 5 years;  $P < .001$ ; 4 vs 1 at 15 years;  $P < .001$ ). Cumulative survival at 15 years was lower in patients with APS than in those without APS (65% vs 90%,  $P = .03$ ). Older age at diagnosis, lupus nephritis, and APS were independent predictors of mortality.

**Conclusions:** Antiphospholipid syndrome with thrombotic manifestations is a major predictor of irreversible organ damage and death in patients with SLE.

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**S**YSTEMIC LUPUS ERYTHEMATOSUS (SLE) is still a significant cause of morbidity and increased mortality.<sup>1</sup> However, relevant changes in the spectrum of lupus complications, both in quantitative and qualitative terms, have occurred in the past decades. Survival rates at 5 years, which were below 70% in early series,<sup>2</sup> are currently higher than 90%.<sup>3,4</sup> Active lupus used to be the main cause of death 30 years ago, but today infections and atherothrombosis are also leading determinants of mortality, particularly after a long disease course.<sup>1</sup> Cardiovascular diseases cause not only death but also substantial morbidity.<sup>5,6</sup>

Antiphospholipid syndrome (APS) is the most important cause of thrombosis in SLE<sup>7</sup> and may be linked to the development of accelerated atherosclerosis.<sup>8</sup> Therefore, many individuals with lupus would be expected to experience long-term complications and even die as a consequence of APS. Some articles published in the early 1990s pointed to the relationship of antiphospholipid antibod-

ies<sup>9,10</sup> and APS<sup>11</sup> with thrombosis and increased mortality in lupus patients.

Recently, new criteria for the classification of definite APS have been proposed by a panel of experts held in Sapporo, Japan, in 1998.<sup>12</sup> Also, the new concept of irreversible organ damage in SLE has been defined as irreversible changes in organ or systems accrued during the course of lupus, although not necessarily caused by SLE (ie, could be the result of treatment or concurrent conditions).<sup>13</sup> In 1996, the Systemic Lupus International Collaborating Clinics–American College of Rheumatology (ACR) damage index (SDI) was created to quantify the degree of irreversible organ damage.<sup>14</sup> The SDI has been subsequently validated<sup>15</sup> and has proved to be predictive of mortality in patients with lupus.<sup>13,15</sup>

Recent prospective series have not analyzed the survival of patients with APS in comparison with those without APS.<sup>3,4</sup> New data also suggest that acute thromboses are not the direct cause of death in all patients with lupus and APS.<sup>16</sup> In addition, whether APS is a cause of irreversible damage in SLE

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is still uncertain. Thus, our aim was to study the impact of definite APS on irreversible organ damage and mortality in patients with lupus.

## METHODS

### STUDY DESIGN

This is an observational study of a prospective inception cohort. Clinical data of patients with SLE attending the Servicio de Medicina Interna at the Hospital de Cruces, Bizkaia, Spain, have been collected and filed in a computerized database. Data filed included demographic variables, clinical manifestations of lupus, autoantibodies, treatments received, and complications of the disease itself and its therapies.

### PATIENTS

All patients who fulfilled at least 4 of the criteria (1982-1997) for the classification of SLE of the ACR<sup>17,18</sup> who entered our cohort between 1973 and 2002 were included in this study. Twenty-six patients were diagnosed as having lupus between 1973 and 1982, 85 between 1983 and 1992, and 91 between 1993 and 2002.

### DATABASE DESIGN

Variables recorded in the database relevant to this study included the following: date of diagnosis; date of last visit; demographics of patients (sex, race, age at SLE diagnosis); clinical manifestations of SLE and antiphospholipid antibodies (anticardiolipin antibodies [aCLs] and lupus anticoagulant [LA]) present within the first 6 months after fulfilling 4 ACR criteria (we called these "at diagnosis"); cumulative clinical features and antiphospholipid antibodies during follow-up; complications of lupus and/or therapy (infections, osteoporosis, fractures, diabetes, and retinopathy); other complications (malignancy); and death and causes of death. Nominal variables were coded in a dichotomous fashion (yes/no).

### DEFINITION OF CLINICAL VARIABLES

To define clinical manifestations of lupus, we used ACR criteria.<sup>17</sup> Thrombosis was only considered in the presence of clinical signs and symptoms and confirmed by image. Any asymptomatic radiological findings at the central nervous system level were not recorded. Small vessel thrombosis needed pathological confirmation.

### ANTIPHOSPHOLIPID ANTIBODY TESTING

Both IgG and IgM aCLs are routinely measured at the immunology laboratory of our hospital using a  $\beta_2$ -glycoprotein I-dependent standardized enzyme-linked immunosorbent assay (ELISA)<sup>19</sup> (Cheshire Diagnostics QACA Kit for IgG/IgM aCL ELISA; Cheshire Diagnostics Ltd, Ellesmere Port, Cheshire, England). In this kit, ELISA plate wells are coated with purified cardiolipin blocked with a solution containing  $\beta_2$ -glycoprotein I. The diluent provided in the kit also contains  $\beta_2$ -glycoprotein I at a concentration of 20  $\mu$ g/mL. Normal aCL limits have been set by the manufacturer at 3 SDs above the mean levels obtained from 115 serum samples of normal blood donors so that titers below 13 IgG phospholipid units (GPL) and 11 IgM phospholipid units (MPL) are considered negative. Titers between 13 and 18 GPL and 11 and 16 MPL are reported as low positive. For this study, we considered as medium high those aCL levels with titers of 20 GPL or MPL or more, according to the limits suggested by international panels.<sup>20,21</sup>

The coagulation laboratory at our hospital tested LA following the guidelines of the International Society on Thrombosis and Hemostasis, Scientific Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies.<sup>22</sup> The phospholipid-dependent clotting tests activated partial thromboplastin time and diluted Russell viper venom time are used as screening tests. Confirmation of the presence of LA is made when the prolongation of the screening tests is corrected by adding reagents with a high concentration of phospholipid (washed platelets) but not by adding normal plasma.

### ANTIPHOSPHOLIPID ANTIBODY AND APS DEFINITIONS

We have used Sapporo definitions.<sup>12</sup> Antiphospholipid antibodies were coded as positive when at least 2 determinations 6 weeks apart were positive for aCL IgG and/or IgM at medium-high levels and/or LA. Patients with only low-titer aCLs or with only 1 positive test result were coded as negative. The diagnosis of APS required positive antiphospholipid antibodies plus documented obstetric and/or thrombotic complications.<sup>12</sup>

### CLINICAL END POINTS

The clinical end points were the presence of irreversible damage accrued during lupus and mortality of any cause. The SDI was used to measure irreversible damage. Forty-one clinical items, divided into 12 domains (ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, gonadal, diabetes, malignancy), were scored if they had been present for at least 6 months. We calculated the SDI at the first 6 months after diagnosis (we called it "at diagnosis") and then at 1, 3, 5, 10, 15, 20, and 25 years of follow-up. All fatalities were recorded. The cause of death was either determined and coded by us, when we certified it or documented from medical records.

### STATISTICAL ANALYSIS

Data filing and statistical calculations were performed using StatView statistical software, version 5.0.1 (SAS Institute Inc, Cary, NC), for Power Macintosh (Apple Computer Inc, Cupertino, Calif). Normality of continuous variables was determined using the Kolmogorov-Smirnov test. Normally distributed variables were summarized using the mean and SD. For nonnormally distributed variables, the median and range were used. Univariate analysis included the  $\chi^2$  test or Fisher exact test, as appropriate, for qualitative variables, the 2-tailed *t* test for continuous variables with normal distribution, and the Mann-Whitney *U* test for continuous variables with nonnormal distribution.<sup>23</sup>

To identify those factors that independently contributed to irreversible damage, we performed a multivariate analysis using backward stepwise logistic regression.<sup>23,24</sup> An SDI score of 1 or higher at 5 years (yes/no) was the dependent variable. Age at diagnosis, sex, lupus nephritis, nonthrombotic central nervous system involvement, lung involvement, thrombosis, APS, and osteoporotic fractures were the independent variables included in the baseline model.

Survival curves were built by the method of Kaplan-Meier and compared using the log-rank test. The time when 4 ACR criteria were met was considered the date of diagnosis and time zero for the purposes of the survival analysis. Finally, we used the Cox proportional hazards regression analysis to investigate the effect of several independent variables on survival.<sup>23,24</sup> We decided to include in the baseline model all variables that we considered clinically meaningful or that have been shown to affect survival in previous studies<sup>1,23</sup>: age at diagno-

sis, sex, thrombocytopenia, lupus nephritis, nonthrombotic central nervous system involvement, lung involvement, thrombosis, infection, and APS. Nonsignificant independent variables were removed from the model using backward stepwise methods. In all regression models, odds ratios (ORs) with 95% confidence intervals (CIs), calculated as the exponential of the regression coefficients, were used as an approximation to relative risks.

## RESULTS

We studied 202 patients. One hundred seventy-eight patients (88%) were women. All patients were white. The mean (SD) age was 36.5 (16.5) years at diagnosis and 46.0 (17.0) years at the end of the follow-up. Mean (SD) follow-up was 9.7 (6.0) years. One hundred fifty-two patients (75%) completed at least 5 years of follow-up, 96 (47%) completed 10 years, 51 (25%) completed 15 years, and 5 (2%) completed 25 years.

Nine patients (4.5%) could not be contacted for follow-up. All of them changed their place of residence and were known to be alive at the time of withdrawing from the cohort. Mean (SD) follow-up of this group was 6.5 (4.0) years. Eight patients (89%) were in the cohort for at least 3 years, and 5 patients (56%) completed at least 5 years of follow-up.

At diagnosis, 135 patients had antiphospholipid antibodies tested. Forty-nine of them (24% of the whole cohort) were positive for aCLs and/or LA. Twelve patients fulfilled criteria for definite APS. During follow-up, antiphospholipid antibodies were tested in 198 patients and detected in 85 of them (**Table 1**). Twenty-eight had APS according to Sapporo definitions.<sup>12</sup> Thrombosis was the clinical criteria met by all patients with APS. Twenty-four patients had arterial events (7 combined with venous thrombosis and 5 combined with small vessel thrombosis), 3 had venous events only, and 1 had isolated small vessel thrombosis (renal thrombotic microangiopathy). Seven women in the group of patients with APS became pregnant after the diagnosis of SLE, 3 of them having obstetric complications (2 fetal deaths and 1 preeclampsia). Two additional women with APS had fetal deaths before the diagnosis of lupus was met.

### IRREVERSIBLE ORGAN DAMAGE

Irreversible organ damage was accrued during disease course. The median (range) SDI scores were 0 (0-5) at diagnosis, 1 (0-6) at 10 years, and 2 (0-6) at 15 years. **Table 2** presents the number of patients with some permanent damage, which increased over the time. Damage was more severe in patients with APS. The median SDI scores in patients with and without APS, respectively, were 2 vs 0 at 5 years ( $P < .001$ , Mann-Whitney *U* test) and 4 vs 1 at 15 years ( $P < .001$ , Mann-Whitney *U* test). Of note, 100% of patients with APS had an SDI score of 2 or higher at 15 years vs 44% of patients without APS ( $P = .005$ , Fisher exact test). This effect of APS on irreversible organ damage was independent of other clinical variables. In a logistic regression model, the adjusted ORs of having an SDI score of 1 or higher at 5 years were 19 (95% CI, 4-93) for patients with APS, 22 (95%

**Table 1. Antiphospholipid Antibodies Detected During Follow-up of 198 Patients**

Antibody	Patients, No. (%)
aCLs* and/or LA	85 (43)
aCLs (IgG)*	73 (37)
aCLs (IgM)*	35 (18)
LA	43 (22)
aCLs* only	41 (21)
LA only†	7 (3)

Abbreviations: aCLs, anticardiolipin antibodies; LA, lupus anticoagulant.

\*Medium-high titers.

†aCL low titer or negative.

**Table 2. SDI Scores During Systemic Lupus Erythematosus\***

Time	SDI Score		
	0	1	≥1
At diagnosis (N = 202)	144 (71)	39 (19)	19 (9)
1 Year (n = 196)	126 (64)	46 (23)	24 (12)
3 Years (n = 178)	99 (56)	47 (26)	32 (17)
5 Years (n = 152)	69 (45)	43 (28)	40 (27)
10 Years (n = 96)	33 (34)	29 (30)	34 (35)
15 Years (n = 51)	11 (22)	13 (25)	27 (53)
20 Years (n = 18)	3 (17)	3 (17)	12 (67)
25 Years (n = 5)	1 (20)	1 (20)	3 (60)

Abbreviation: SDI, Systemic Lupus International Collaborating Clinics–American College of Rheumatology damage index.

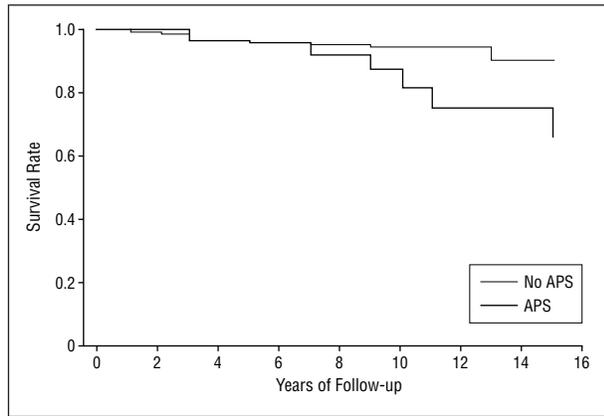
\*Data are presented as number (percentage) of patients. Because of rounding, percentages may not total 100.

CI, 2-193) for patients with osteoporotic fractures, and 10 (95% CI, 4-23) for patients with lupus nephritis.

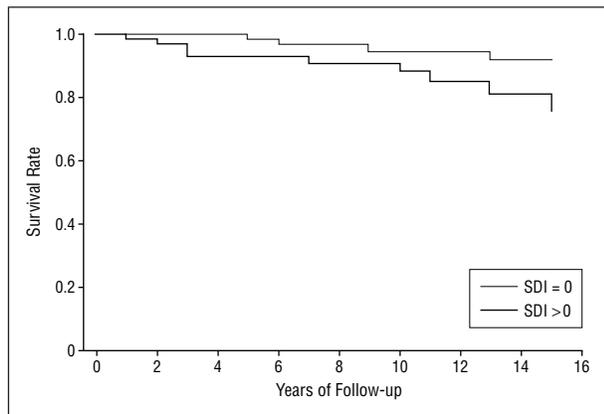
### SURVIVAL ANALYSIS

Twenty-two patients (11%) died during the follow-up. Eighteen (81%) of them were women. Mean (SD) age at the time of death was 54 (19) years. Mean (SD) time of follow-up was 9.7 (6.3) years. Eight patients (36%) died within the first 5 years after diagnosis, 9 (41%) between 6 and 15 years, and 5 (23%) after 15 years of disease. Cumulative survival of the complete cohort was 95% at 5 years, 91% at 10 years, 86% at 15 years, 69% at 20 years, and 55% at 25 years. Given the small number of patients at risk beyond 15 years of follow-up, we decided to limit survival comparisons to that point.

Eight patients (36%) fulfilled Sapporo criteria for definite APS before dying. In 4 of these patients, thrombotic events could have been the direct cause or a major predisposing factor for death (mesenteric ischemia, sudden death, atherosclerotic disease, and heart failure). None of them were receiving anticoagulant treatment at the time of their death. Two patients died before prolonged oral anticoagulation was considered the standard treatment for patients with APS and thrombosis.<sup>25</sup> Two patients with previous arterial thrombosis were taking antiaggregants without evidence of new acute thrombotic events until progressive heart failure and widespread atherosclerosis led to death. Of the remaining 4 patients with APS, 2 died of cancer, 1 died of infection (legionellosis), and 1 committed suicide. Causes of death in patients without



**Figure 1.** Cumulative survival at 15 years for patients with (n=28) and without (n=174) antiphospholipid syndrome (APS) ( $P=.03$  for the difference, log-rank test).



**Figure 2.** Cumulative survival at 15 years for patients with (n=70) and without (n=126) a Systemic Lupus International Collaborating Clinics–American College of Rheumatology damage index (SDI) score of 0 or higher at 1 year ( $P=.02$  for the difference, log-rank test).

APS were infections (n=4), cardiovascular events (n=3), pulmonary hypertension (n=2), cancer (n=1), liver failure (n=1), respiratory failure (n=1), suicide (n=1) and unknown (n=1).

Kaplan-Meier survival curves of patients with and without APS are shown in **Figure 1**. Both curves began to diverge at 10 years (cumulative survival, 80% vs 94%;  $P=.20$ ; log-rank test) and the difference became significant at 15 years (cumulative survival, 65% vs 90%;  $P=.03$ , log-rank test).

Patients with some degree of irreversible organ damage also showed increased mortality (**Figure 2**). Cumulative 15-year survival was 76% in patients with an SDI score of 1 or higher at 1 year compared with 92% in patients without any damage at that point ( $P=.02$ , log-rank test).

Several variables were included in a Cox proportional hazards regression model to determine the independent predictors of survival at 15 years (see “Methods” section). The final model included 3 explanatory variables: age at diagnosis (OR, 1.07; 95% CI, 1.03-1.1), renal involvement (OR, 4.4; 95% CI, 1.4-14.0), and APS (OR, 3.9; 95% CI, 1.4-11.3). The noninclusion of APS in the baseline model made thrombosis a significant fi-

nal explanatory variable, which suggests that the influence of APS on survival is dependent of thrombotic manifestations.

## COMMENT

Our results show that APS is an important predictor of irreversible organ damage and mortality in patients with SLE. Increased mortality linked to APS is due to thrombosis, as a consequence of both acute events and irreversible organ damage. Thus, the subgroup of patients with definite APS has been identified as high risk among those with SLE.

Mortality rates and causes of death have been similar in our cohort and other recent series.<sup>3,26</sup> Cumulative survivals of 95% and 85% have been seen at 10 and 15 years, respectively. Infection and cardiovascular diseases were the most frequent conditions that led to death. However, we have observed few patients dying of active lupus. A progressive increase of irreversible organ damage was seen in our cohort. More than half of the patients had some degree of damage after 5 years of disease, and 53% had an SDI score of 2 or higher at 15 years. We have also shown that higher SDI scores lead to increased mortality, which is in agreement with the results reported by other authors.<sup>15</sup>

We found a strong effect of APS on mortality of patients with SLE, confirming results of the study by Drenkard et al.<sup>11</sup> Although those patients with definite APS were only 14% of the total cohort, the difference in survival rates seen between groups with and without APS (65% vs 90% at 15 years) was high enough to reach statistical significance. Indeed, APS was identified as an independent risk factor for mortality, together with age and lupus nephritis, 2 well-known adverse prognostic variables in lupus.<sup>3,4,10</sup> Other clinical manifestations previously associated with increased mortality in lupus patients, such as thrombocytopenia and lung involvement,<sup>4</sup> were not significant in this cohort.

Given the importance of thrombosis among the causes of death reported in recent prospective studies,<sup>3,4</sup> our results are not surprising. Indeed, 3 previous works also pointed in this direction. Jouhikainen et al<sup>9</sup> studied the course of 37 patients with SLE and LA and 37 age- and sex-matched lupus controls without LA. They found a higher incidence of deep vein thrombosis among patients with LA and increased mortality related to both deep vein thrombosis and LA positivity. Gulko et al<sup>10</sup> studied 139 patients with SLE to determine the impact of several variables on survival. They found that aCL positivity and thrombosis, together with renal failure, age, and infection, were major predictors of mortality. Drenkard et al<sup>11</sup> found APS, as defined by the criteria proposed by Alarcon-Segovia et al,<sup>27</sup> predictive of mortality in a cohort of 667 Mexican patients with SLE. In our study, thrombosis, highly dependent on the presence of APS, was also identified as an adverse prognostic variable.

However, thrombosis was the direct cause of only part of the deaths of lupus patients with APS. This observation has also been made by other authors.<sup>16</sup> Therefore, APS exerts an adverse impact on the course of SLE in addition to the effect of fatal acute thrombosis. In our

study, APS was a strong and independent cause of irreversible damage, which was also a predictor of death. It is probable that, apart from the inherent high risk of end-stage organ failure, permanent damage may make patients more prone to experience complications, such as infections and drug toxic effects (and maybe cancer), leading to death.

This study has some limitations. The first is that arterial thromboses were the clinical manifestations associated with APS in most patients. Thus, patients in our group had a particularly severe form of APS. It is likely that the impact of APS on mortality and damage would be less in people with other clinical manifestations.

The second problem is the relatively small number of patients included in our study. We had to limit the extension of the survival analysis to 15 years due to the small group of patients followed up beyond that point. Also, we obtained wide 95% CIs of the ORs, resulting from multivariate analyses with the consequent increase of uncertainty. However, all the lower limits of the 95% CIs were clearly greater than 1, which suggests a clinically meaningful effect of significant variables.

Finally, because this study was observational, no specific interventions in terms of therapy were planned. Some patients with APS and thrombosis did not receive prolonged oral anticoagulant treatment. This is especially true in patients treated before 1995, when it became clearly established that vitamin K antagonists are the drugs of choice for this group of patients.<sup>25</sup> Whether the effect of APS on mortality and organ damage would have been the same had all patients with thrombosis been taking warfarin sodium is not possible to address. However, a more benign clinical course in this scenario is likely.

However, our study is free from other possible biases. We analyzed a prospective inception cohort in which few patients were lost to follow-up, most of them after several years of disease course. This reduces the bias associated with early deaths that are not analyzed due to either late inclusion in the cohort or high numbers of missing patients.<sup>2</sup> Besides, causes of death were documented in all but 1 patient, most of them being attended by us at the time of their death.

This study confirms the role of APS as a major cause of morbidity and mortality in patients with SLE, at least when associated with arterial thrombotic manifestations. Other studies have shown thrombotic recurrences in patients receiving only antiaggregants<sup>25</sup> or anticoagulation therapy to an international normalized ratio below 3.0.<sup>25,28</sup> Also, the low risk of fatal bleeding in patients with APS receiving warfarin to a target international normalized ratio of 3.5 has been shown.<sup>28</sup> Accordingly, early anticoagulant treatment is mandatory after the first thrombotic event in lupus patients with antiphospholipid antibodies. High-intensity anticoagulation therapy is indicated in patients with arterial events,<sup>7,28</sup> whereas a lower international normalized ratio could be targeted in those with venous thrombosis only.<sup>7</sup>

However, the first thrombosis may also cause death or severe permanent damage. Thus, primary prophylaxis, which already has been recommended for patients with SLE and antiphospholipid antibodies,<sup>29</sup> is supported by our data. A randomized clinical trial currently underway will help

determine whether aspirin is enough or should be combined with low-dose oral anticoagulants.<sup>30</sup> In addition, strict control of other risk factors for thrombosis should be accomplished in all patients with SLE and especially in those with antiphospholipid antibodies.<sup>28</sup>

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#### Announcement

##### New Editor and New Address for Editorial Correspondence

**E**ffective January 2004, Philip Greenland, MD, succeeds James E. Dalen, MD, MPH, as Editor of the ARCHIVES. Editorial correspondence can be sent to the new address: Philip Greenland, MD, Editor, *Archives of Internal Medicine*, 680 N Lake Shore Dr, Suite 1102, Chicago, IL 60611; phone: 312-503-5387; fax: 312-503-5388; e-mail: archinternmed@jama-archives.org. Manuscript submissions should be sent to Dr Greenland's attention via e-mail attachment to archintermed@jama-archives.org.