ACS, consisting of unstable angina and acute myocardial infarction with or without ST-segment elevation, was based on clinical, electrocardiographic and angiographic presentations and cardiac enzyme tests, correlating with the duration and extent of coronary occlusion as a consequence of plaque rupture.

There were 109 patients with unstable angina and 145 patients with acute myocardial infarction. Blood samples withdrawn before heparin treatment as the baseline, 24 h later, at the end of heparin treatment and at 4 weeks, respectively, were used for tests of the platelet count and HIT antibodies in addition to routine chemical laboratory tests. PCI was performed in 165 patients, with a success rate of potency of 98%. Heparin was administered intravenously to achieve optimal anticoagulation under the activated partial thromboplastin time (APTT), targeting a value of 1.5–2.5 times the baseline. The combined use of antiplatelet drugs was employed in 96.0% of 254 patients. Aspirin was used with ticlopidine and/or cilostazol in an estimated 71.7% of patients (Table 1).

Hematological analysis, including the platelet count, was performed at the same time as the blood sampling. Serum samples were frozen immediately and stored at −70 °C until completion of the HIT antibody test. The HIT antibody titer was measured with a sandwich-type ELISA (Asserachrom, HPIA, Stago, France), according to the instructions of a kit that detected HIT antibodies including IgG, IgA and IgM isotypes. While the results of the ELISA test merely confirm the presence of HIT antibody, HIT was defined as a >50% reduction in the platelet count or an absolute platelet count of $<100\times10^9$/L during and after heparin treatment with no other cause of thrombocytopenia and a positive result in the HIT-antibody test corresponding to thrombocytopenia. As the ELISA carried a high rate of false-positive results, a positive patient without HIT-related thrombocytopenia was not suspected of having HIT [9]. When a patient with HIT showed thromboembolic development, it was evaluated whether the development was compatible with HIT-associated thrombosis or not.

Clinical outcomes, including death and thromboembolic developments, were studied. Thromboembolic development associated with or without HIT was evaluated by clinical and echoradiographic imaging, and was classified into venous, arterial and cardiac thrombosis. Cardiac thrombosis was subclassified into subacute coronary thrombosis, new or recurrent myocardial infarction and intracardiac thrombosis. Bleeding episodes from arterial or venous puncture sites and intracranial, gastrointestinal and genitourinary tracts were recorded for 4 weeks. A statistical analysis was conducted. Paired continuous variables were compared using the paired *t* test. Categorical variables were compared using the chi square test, and odds ratios with confidence intervals (CI) are presented. All statistical tests were two-sided, and significance was defined as $p<0.05$.

Table 1 Clinical characteristics of 254 patients

Age (mean±S.D., year old)	66.4±11.4
Sex, *n* (%)	
Male	205 (80.7%)
Female	49 (19.3%)
Details of ACS, *n* (%)	
Unstable angina pectoris	109 (42.9%)
Acute myocardial infarction	145 (57.1%)
PCI performed, *n* (%)	
Performed	165 (65.0%)
Not performed	89 (35.0%)
Heparin application (mean±S.D.)	
A bolus dose ($\times10^4$ IU)	0.9±0.2
Maintenance dose (×IU/kg/h)	8.1±2.4
Days of infusion	5.0±3.0
Mean APTT prolongation(times baseline)	2.3±1.6
Previous heparin history, *n* (%)	63 (24.8%)
Combined use of drugs, *n* (%)	
Antiplatelet drug:	244 (96.0%)
Aspirin	61 (24.0%)
Aspirin+ticlopidine or cilostazol	123 (48.4%)
Aspirin+ticlopidine+cilostazol	52 (20.5%)
Others (dipiridamole or sarpogrelate)	13 (5.1%)
Tissue plasminogen activator	30 (11.8%)
Warfarin	21 (8.3%)

ACS: acute coronary syndrome.
APTT: activated partial thromboplastin time.
PCI: percutaneous coronary intervention.

Results

There was no correlation between platelet counts and the titers of HIT antibodies, and there was no significant decrease in platelet counts associated with the seroconversion during the study term. Two patients already had a positive HIT titer before heparin treatment and were excluded from the analysis. At the end of the infusion period (5.0±3.4 days, mean±S.D.), eight patients had become positive. While off heparin, 14 patients were newly found to be positive. Thus, a total of 22 patients (8.7%, 95% CI: 5.9–13.1) seroconverted during the study term. The median optical density (OD) of HIT antibodies determined by ELISA in the seroconverted patients had also increased at the end of heparin infusion and further 4 weeks later (Fig. 1).

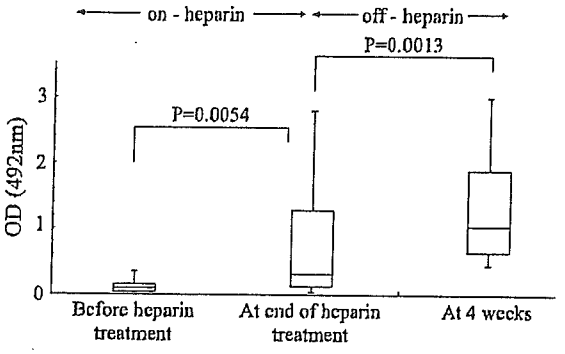

Figure 1 Median optical density (OD) of heparin-PF4 complex antibodies in patients on and off heparin infusion. n=22, excluding two patients having preexisting HIT antibodies. Box plots indicate the median, interquartile range (25–75%) and outliers (min, max).

It was examined whether there was a new or exacerbating thromboembolism between seroconverted and nonconverted patients. Thromboembolic developments were found significantly more often in the 22 seroconverted rather than the 230 nonconverted patients. The odds ratio of risk for thrombotic developments during the study term rose to 17.4 (95% CI: 5.2–58.4) in seroconverted patients compared with nonconverted patients (Table 2). Thromboembolic developments in seven seroconverted patients occurred during the period of heparin infusion rather than cessation of heparin treatment (25.0 vs. 0.9%, p<0.001). Among the 22 patients who showed seroconversion, four developed thrombocytopenia with a 50% reduction in platelet counts from the baseline as a clear sigh of HIT. Two of these four patients who developed thrombotic events (one, coronary stent thrombosis; the other, myocardial infarction) were diagnosed as having HIT with thrombosis. Of the other five seroconverted patients with thromboembolic developments, two suffered from thromboembolic events (one, subacute coronary stent thrombosis; the other, recurrent myocardial infarction) on the first day in the hospital, and another two patients developed recurrent myocardial infarction on the third day after the heparin infusion. However, they did not show any drop in the platelet count, and their HIT antibodies remained negative at the time of these events. One seroconverted patient developed an ischemic stroke without thrombocytopenia 13 days after the heparin treatment ceased. These five patients could be excluded as having definite HIT because of neither HIT-compatible thrombocytopenia nor seroconversion. Of six nonconverted patients who showed no drop in the platelet count comparable to HIT, five were treated with PCI and subsequently developed thromboembolism (two, recurrent myocardial infarction; one, stent thrombosis, intracardiac thrombosis, ischemic stroke, respectively). The other patient who received no PCI developed myocardial infarction from an unstable angina.

Table 3 Factors affecting the rate of seroconversion in 252 ACS patients

Factors	N	Seroconversion rate (%)	Odds ratio (95% CI)	p-value
PCI				
Not performed	89	2.3	6.1 (1.4–26.7)	0.009
Performed	163	12.3*		
Underlying disease				
Unstable angina	107	3.7	3.6 (1.2–11.1)	0.022
Myocardial infarction	145	12.4*		
Period of heparin treatment				
<5 days	122	4.1	3.5 (1.3–9.9)	0.014
≧5 days	130	13.1*		
Thrombotic history				
No thrombosis	207	6.8	3.0 (1.2–7.6)	0.035
Thrombosis	45	17.8*		
Complications				
Normolipidemia	187	6.4	2.7 (1.1–6.5)	0.039
Hyperlipidemia	65	15.4*		
Nondiabetic	181	6.6	2.3 (1.0–5.6)	0.081
Diabetes mellitus	71	14.1		
Age				
<70 years	136	8.8	1.0 (0.4–2.4)	1.000
≧70 years	116	8.9		

* p<0.05.

Odds ratios were calculated to identify factors affecting the seroconversion in ACS (Table 3). Aging itself did not facilitate the seroconversion. The highest odds ratio, 6.1 (95% CI: 1.4–26.7), was obtained in ACS patients treated with PCI. The infusion of heparin for over 5 days (odds ratio, 3.5,

Table 2 Comparison of thromboembolic development rate between seroconverted and nonconverted patients

	Seroconverted n (%): 22 (100)	Nonconverted n (%): 230 (100)	Odds ratio (95% CI)	p-value
Thromboembolic development	7[a] (31.8)	6 (2.6)	17.4 (5.2–58.4)	<0.0001

[a] Includes two patients having HIT with thrombosis.

95% CI: 1.3–9.9), myocardial infarction as an underlying disease (odds ratio, 3.6, 95% CI: 1.2–11.1), hyperlipidemia (odds ratio, 2.7, 95% CI: 1.1–6.5) and diabetic complications (odds ratio 2.3, 95% CI: 1.0–5.6) all facilitated the seroconversion. In 45 patients having a thrombotic history, including cerebrovascular (n=9), cardiovascular (n=33) and peripheral vascular diseases (n=3), the odds ratio was estimated at 3.0 (95% CI: 1.4–26.7).

In a multiple-logistic regression analysis of factors affecting the seroconversion rate, significantly adjusted odds ratios were obtained for PCI (adjusted odds ratio; 6.5, 95% CI: 1.5–29.1, p=0.014) and over 5 days heparin infusion (4.3, CI: 1.5–12.4, p=0.008), respectively. Therefore, both the PCI procedure and over 5 days heparin infusion were important factors contributing to the seroconversion.

Seroconversion rates in 163 ACS patients who underwent PCI increased significantly to 18.3% when the patients received heparin for over 5 days (p=0.030). In the PCI patients who had a thrombotic history, hyperlipidemia, diabetes mellitus or either underlying disease, each factor contributing to the seroconversion increased compared with that in PCI patients associated with none of these factors (Table 4). The increased risk of seroconversion in the group who underwent PCI was characteristic when ACS patients having one of these factors were treated with the PCI procedure. Overall outcome was estimated with three deaths due to cardiogenic shock in 230 nonseroconverted patients. Six bleeding episodes from four gastrointestinal tracts and two arterial puncture sites were also found, including two patients on heparin and four patients off heparin, among the nonseroconverted patients.

Table 4. Factors affecting the rate of seroconversion on heparin treatment in 163 patients with PCI

Factors	N	Seroconversion rate (%)	Odds ratio (95% CI)	p-value
Period of heparin treatment				
<5 days	81	6.2	3.4 (1.2–9.9)	0.030*
≧5 days	82	18.3		
Thrombotic history				
No thrombosis	131	9.9	2.5 (0.9–7.0)	0.075
Thrombosis	32	21.9		
Complications				
Normolipidemia	115	9.6	2.2 (0.8–5.7)	0.120
Hyperlipidemia	48	18.8		
Nondiabetic	109	10.1	1.9 (0.7–4.6)	0.310
Diabetes mellitus	54	16.7		
Underlying disease				
Unstable angina	44	6.8	2.3 (0.6–8.1)	0.284
Myocardial infarction	119	14.3		

* p<0.05.

Discussion

The seroconversion rate measured by ELISA and the clinical characteristics of 254 ACS patients treated with heparin were studied. Two subjects having preexisting HIT antibodies were excluded from the analysis. The seroconversion rate in the remaining ACS patients was estimated at 8.7% 4 weeks after the start of heparin treatment. Twenty-two patients became positive, and four patients, including two with thrombosis, developed HIT during the study term. The incidence of thromboembolic development was significantly higher in seroconverted patients than nonconverted patients. HIT antibodies have a characteristic binding affinity for PF4 in a complex with heparin-like molecules on the endothelium and generate the expression of tissue factor. And the occlusion of the coronary artery after PCI could be brought about by interaction with tissue factor in atheroma and platelets leading to the generation of prothombinase and thrombin [10]. It is possible that HIT antibodies in seroconverted patients induce the production of thrombin through the expression of tissue factor, and the HIT antibodies themselves might be a cause of thrombophilia.

Seroconversion increases the chance of a complex forming with PF4 under optimal conditions with heparin as a source of the antigen. As HIT antibodies were found in 17% of patients treated with heparin for more than 7 days, the presence of HIT antibodies in patients with heparin therapy has been concluded to predict the risk of developing HIT unless the antibodies become negative [11]. Therefore, a longer infusion of heparin may precipitate the chance of seroconversion. The incidence of seroconversion in patients with deep vein thrombosis treated with heparin increased from 9.1% on day 5–7 to 20.1% on day 21. Also, positive seroconversion increased in accordance with the duration of treatment with low molecular weight heparin [12]. Although seroconversion rates of 27–50% were reported among patients undergoing cardiac surgery [13–15], the incidence of HIT appeared to be less than 2% [16]. In the present study, the incidence of HIT was 1.6%, a figure similar to that

for cardiac surgery, although the rate of seroconversion following cardiac surgery is much higher than 8.7% in ACS patients. The incidence of serologically confirmed HIT in 358 heparin-treated patients, including those with heart or cerebrovascular diseases, was very low (0.3%), and there were 30 seroconverted patients with no thrombocytopenia, a rate of 8.4% [17].

In this study, 20 of 22 seroconverted patients underwent PCI with heparin anticoagulation. PCI requires an adequate heparinization to avoid thrombosis caused by endothelial disruption due to catheter manipulation during the procedure. PCI with adequate heparinization leads to a state of hypercoagulability during and after the intervention [18]. In addition to the PCI-induced endothelial disruption, HIT antibodies might evoke tissue factor expression through immunological injury, resulting in platelet to platelet interaction and endothelial hyperplasia. Endothelial hyperplasia is suggested to contribute to the growth of a thrombus in HIT [19]. In the present study, PCI was the main factor facilitating seroconversion. Other affecting factors included heparin treatment for over 5 days, a thrombotic history and hyperlipidemia.

However, an early cessation of heparin treatment after the onset of thrombocytopenia has been shown to be ineffective against morbid events in HIT patients [20]. In the present study, the seroconversion rate and titer were found to increase in patients on and off heparin, and the risk of developing HIT continued after the cessation of treatment. It is unclear whether a seroconverted patient in whom the cause of a sudden drop in the platelet count is unknown should be treated with an alternative anticoagulant. However, during PCI in patients with HIT, argatroban is a reasonable alternative [21]. PCI with heparin could lead to a positive seroconversion in the presence of one or more of these affecting factors, and the duration of treatment with heparin had a significant effect on seroconversion in PCI patients. It is suggested that PCI, duration of heparin treatment, thrombotic history and hyperlipidemia have a booster effect on the heparin-induced seroconversion.

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LETTERS TO THE EDITOR

ANOTHER DATA/RHETORIC MISMATCH ON DONEPEZIL

To the Editor: Lopez et al. report that "cholinesterase inhibitor (CEI) use had a clinically meaningful effect on the natural history of Alzheimer Disease (AD)," slowing disease progression and lowering risk of nursing home admission after 2 years.[1]

The design of the study is worrisome. Of 1,139 patients who enrolled in the AD Research Center over 7 years, 270 were selected; 135 began taking CEIs "immediately after enrollment, and continued to take them throughout the following 12 months," and 135 never took the drug. How these individuals were selected is not otherwise described. They were matched on a few characteristics, such as age, Mini-Mental State Examination score, and education.

This study resembles a study by Dr. Geldmacher et al. that showed that patients who took a CEI faithfully (80% of pills or more) had a significant delay in nursing home placement (NHP).[2] Both of these nonrandomized studies failed to report important baseline characteristics of the groups being studied. In the Geldmacher article, for example, nonadherent patients were far less likely to have a spouse caregiver than faithful users,[3] yet the authors, who claimed it was the donepezil that "resulted in significant delays in NHP," omitted this fact.[2]

Both papers are easily distinguished from AD 2000,[4] a properly randomized, controlled trial with the largest number of placebo-controlled patient-years of any cholinesterase study.[5] In AD 2000, "no significant benefits were seen with donepezil compared with placebo in institutionalization or progression of disability . . . [or] in behavioral and psychological symptoms, carer psychopathology, formal care costs, unpaid caregiver time, adverse events, or death or between 5 mg and 10 mg of donepezil."[4] In the United Kingdom, the National Institute for Clinical Excellence Appraisal Committee has recently issued the following preliminary recommendation: "Donepezil, rivastigmine and galantamine are not recommended for use in the treatment of mild to moderate Alzheimer's disease (AD)."[6]

Would Dr. Lopez modify the discussion of his paper, where he emphasizes the important benefits of donepezil, in view of the results from AD 2000, a larger, better-designed trial that failed to show any meaningful difference at all?

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RESPONSE TO DR. FINUCANE

To the Editor: We previously addressed Dr. Finucane's critique of our article.[1,2] We will therefore focus on his comparisons of our article to the work of Dr. Lopez et al.[3] and the AD 2000 trial.[4] Our study and the Lopez et al. study both support a role for cholinesterase inhibitors in the treatment of Alzheimer's disease (AD), specifically as they pertain to delayed nursing home placement. Otherwise, even a cursory review reveals considerable differences in the research paradigm, funding agency, subject ascertainment, and analytical methods between studies.

Dr. Finucane repeats the incorrect assertion that we omitted differences in caregiver characteristics from our report. We explicitly state on p. 940 that caregiver type (spouse vs nonspouse) was included as a covariate in our analysis and that there were no statistically significant differences in the proportion of spousal caregivers across our exposure groups.[2]

We concur with Dr. Finucane that our study and the report by Dr. Lopez et al. are both easily distinguished from the AD 2000 trial, but Dr. Finucane fails to acknowledge major methodological shortcomings of the AD 2000 trial, including the facts that systematic diagnosis of AD was not required for entry into that study, investigators were instructed to enroll only subjects in whom treatment response could not be predicted (excluding those patients who were likely to show a treatment response), and marked underenrollment and excessive attrition rates were likely to have exerted significant biases on the interpretation of the data. Dr. Finucane's uncritical endorsement of the AD 2000 conclusions also does not acknowledge the approximately 70%

0002-8614/05/$15.00

likelihood of a Type II statistical error in the published interpretation, by which an actual effect would be undetected by the analysis as conducted.[5]

Although openly critical of studies associated with the pharmaceutical industry, Dr. Finucane fails to note the substantial risk for sponsor bias in AD 2000, which the principal payor for medications in the United Kingdom funded. Dr. Finucane also omits mention of the incomplete status of the proposed revision from the recently renamed National Institute for Health and Clinical Excellence regarding medications for Alzheimer's disease. The text accompanying the revision explicitly states: "Note that this document does not constitute the Institute's formal guidance on this technology. The recommendations made in Section 1 are preliminary and may change after consultation."[6]

Dr. Finucane's assertion of a data/rhetoric mismatch therefore appears to apply quite well to his own criticism of treatments for Alzheimer's disease.

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Author Contributions: David S. Geldmacher, George Provenzano, Thomas McRae, and John R. Ieni all contributed equally in preparing this response.

Sponsor's Role: Eisai, Inc. and Pfizer, Inc. sponsored the study that Dr. Finucane cites,[2] but there was no sponsorship associated with the preparation of this response.

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RESPONSE LETTER TO DR. THOMAS FINUCANE

To the Editor: We appreciate Dr. Finucane's letter regarding our paper published in the Journal of the American Geriatrics Society in January 2005.[1] The methodology of our observational study was reported, at length, in a previous publication.[2] The study was conducted in 135 patients with probable Alzheimer's disease (AD) who used cholinesterase inhibitors (CEIs) for at least 1 year and who were matched using Mini-Mental State Examination scores, age, duration of the dementia symptoms, and education level with a nontreated group, which allowed us to increase the statistical power. Furthermore, the nontreated subjects were enrolled contemporaneously to the treated group. This is particularly important because referral sources vary over time, and patients in the late 1980s and early 1990s did not receive the same medical treatment as those in the late 1990s (e.g., 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors, angiotensin-converting enzyme inhibitors). This cohort reflected the experience of a memory clinic during the 1990s, where some subjects with AD were reluctant to initiate any type of treatment.

Although our results were similar to the study conducted by Geldmacher et al.,[3] the methodology was different. Those authors classified the subjects as "minimal-use," "early moderate-use," "delayed-start," or "maximal-use" based on the medication they received during the placebo-controlled and open-label phases and found a delay in nursing home (NH) admission in those classified as "maximal-use" compared with the "minimal-use" group. In our study, all subjects used CEIs from study entry through last contact or death.

We welcome the opportunity to comment on the AD 2000 trial,[4] which had serious methodological problems that make its results difficult to interpret. This study recruited only individuals whose treating physicians were uncertain about the benefits of the treatment, 16% had vascular dementia, and there was a high attrition rate; 48% dropped out during the first 48 weeks, and only 0.7% completed the 3 years of follow-up. The majority of the critical events occurred within the first 48 weeks of the study (49 of 85 (58%) of the NH admissions and 36 of 48 (75%) of the deaths), suggesting that these individuals were severely impaired. By contrast, none of the patients in our study went to a NH during the first year of follow-up, and 25.5% died during a mean follow-up of 3.5 years. Thus, the AD 2000 study had a highly biased sample, and the follow-

up rate was quite low, especially compared to our[1] or Geldmacher et al's study.[3]

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DELAYED REFLECTION PRESSURE WAVE: NEW ASPECTS FOR POSTPRANDIAL HYPOTENSION

To the Editor: Postprandial hypotension (PPH), a potent risk factor for dizziness, syncope, and falls,[1] is common in elderly persons.[2] Recently, a higher incidence of coronary events, stroke, and total mortality was reported in PPH subjects.[3] A significant association has also been reported between PPH and asymptomatic cerebrovascular damage.[4] A prevalence of PPH, defined as a more than 20-mmHg decline in systolic blood pressure (BP), has been estimated at 24% to 36% in elderly persons living in nursing homes.[5,6] In elderly patients with cardiovascular disease and hypertension, the prevalence is thought to be greater.[2,7] Decreased distensibility of the aorta is one of the major mechanisms of elderly hypertension. An augmentation of arterial pressure by early return of the reflection pressure wave is thought to be another underlying mechanism.[8] Recently, a significant association has been reported between the decreased augmented pressure and orthostatic hypotension.[9] In the present study, the relationship between reduced augmented pressure, caused by a delayed return of reflection pressure wave, and PPH was evaluated in healthy, community-dwelling elderly subjects.

The study subjects consisted of nine elderly women and nine young women recruited from the Shimanami Health Promoting Program cohort.[10] All subjects were free from any antihypertensive treatment and had no known history or symptoms of cardiovascular diseases. Brachial BP was measured in the supine position using a cuff-oscillometric device (form PWV/ABI, Colin Co. Ltd., Aichi, Japan). The carotid arterial pressure waveform was measured using a tonometric tracing simultaneously. Carotid BP and the augmentation index (AIx) were then calculated from the pressure waveform.[9] The AIx is the ratio of augmented pressure to pulse pressure. Larger AIx values indicate increased wave reflection from the periphery or an earlier return of the reflected wave as a result of increased arterial stiffness. Pulse wave velocity (PWV) was also determined as the phase contrast between the brachial waveform and the ankle waveform. All measurements were conducted at 5 minutes before and 30 minutes after lunch, and the difference between the two measurements was considered to be the postprandial change.

Table 1 summarizes the postprandial changes in the brachial and carotid hemodynamics. In the elderly subjects, brachial and carotid systolic BP, as well as mean BP and diastolic BP, were significantly lower after lunch. Carotid AIx and arterial PWV, one of the regulatory factors for carotid AIx, were also lower after lunch. The lower AIx indicates the attenuation of augmented pressure by the reflection pressure wave. Although splanchnic blood pooling appears to be an important initial event in the development of postprandial hypotension, the postprandial decline in the augmented pressure may cause further decline in carotid systolic BP.

The postprandial changes in AIx were significantly associated with the reduction of carotid systolic BP in elderly subjects (correlation coefficient $(r) = 0.67$, $P = .049$). No associations were observed in young subjects ($r = 0.07$, $P = .86$), although carotid AIx was significantly lower after lunch (Table 1). In the young subjects, basal and postprandial carotid AIx were negative, which indicates the lack of augmented pressure. The lack of augmented pressure was partially associated with the absence of postprandial changes in systolic BP in spite of the mild to moderate reduction of mean BP and diastolic BP. In the elderly subjects, the higher basal AIx, representing greater arterial stiffness, could be one of the underlying mechanisms of the development of postprandial hypotension.

This is the first study representing the significant association between enhanced arterial stiffness, as well as delayed reflection pressure wave, and postprandial BP decline. These findings contain several important aspects

Table 1. Postprandial Changes in Brachial and Carotid Hemodynamics

Characteristic	Young Subjects (n = 9)			Elderly Subjects (n = 9)		
	Preprandial	Postprandial		Preprandial	Postprandial	
	Mean ± SD		*P*-value	Mean ± SD		*P*-value
Age (range)	21 ± 1 (20–21)			67 ± 3 (64–73)		
Body mass index, kg/m^2	21 ± 2			23 ± 3		
Brachial systolic BP, mmHg	108 ± 2	109 ± 4	.68	122 ± 17	114 ± 18	.01
Carotid systolic BP, mmHg	109 ± 7	111 ± 5	.41	119 ± 21	111 ± 22	.03
Mean BP, mmHg	80 ± 4	77 ± 3	.09	95 ± 14	87 ± 14	.009
Diastolic BP, mmHg	65 ± 2	61 ± 4	.03	76 ± 11	68 ± 11	<.001
Carotid augmentation index, %	−3 ± 13	−19 ± 11	<.001	41 ± 6	32 ± 7	.004
Brachial-ankle pulse wave velocity, cm/sec	1,004 ± 93	890 ± 69	.001	1,421 ± 338	1,343 ± 245	.12
Heat rate, beat/min	57 ± 10	64 ± 9	.01	58 ± 6	62 ± 4	.04

Note: Statistical significance was analyzed using paired *t* test.
SD = standard deviation; BP = blood pressure.

that help further understanding of BP dysregulation in the elderly subjects.

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IS ESTABLISHING AN APPROPRIATE BLEEDING RISK PROFILE IN ELDERLY PATIENTS TREATED WITH LOW-MOLECULAR-WEIGHT HEPARINS NEEDED?

To the Editor: We have read with interest the report by Conde et al.[1] and would like to comment on some interesting points. Briefly, the authors reported a retrospective series of geriatric patients who developed retroperitoneal hematomas after receiving treatment with low-molecular-weight heparin (LMWH). All patients were aged 70 and older. Twelve of 15 cases (75%) received an anticoagulant dose of LMWH (a high dose). Ten patients (66%) received, antiplatelet drugs simultaneously, and seven (50%) had an increased serum creatinine value.

Aging, high dose, renal-function impairment, and concomitant use of drugs affecting hemostasis are the most-classic and best-known risk factors for bleeding in patients receiving LMWH.[2] The authors state that "most of the patients described had a potential risk factor for bleeding"; but it may be more appropriate to say that this series had a high, or perhaps, very high risk profile for hemorrhagic events, although a cumulative risk profile for each patient was not

provided. Thus, the designation as "spontaneous" to retroperitoneal hematomas in their series may be questioned.

Almost half of the cases (7 patients) had elevated serum creatinine level. The presence of cardiovascular risk factors such as hypertension (8 patients) and diabetes mellitus (4 patients) may explain this unexpected high frequency of renal insufficiency, but the authors make no reference to what the creatinine clearance (CrCl) in the other eight patients was. This information is significant because the authors discuss the fact that a "normal serum creatinine value" does not exclude a reduced CrCl. Another study[3] revealed that measured CrCl was low in a series of 26 elderly patients despite a normal serum creatinine level. Other authors have confirmed this.[4,5] Decreased CrCl has been associated with increased hemorrhagic risk.[5] Renal function plays an important role in the clearance of LMWH, and a dose adjustment (up to 65% of the recommended dose) may be necessary in patients with reduced CrCl ($\leq$30 mL/min) receiving enoxaparin to reduce bleeding risk.[6,7] Conde et al.[1] did not indicate whether such dose adjustment was given to their patients.

Finally, the authors state that "anti-Factor-Xa activity should be monitored in high-risk patients receiving LMWH," but this has been questioned previously because bleeding events could appear in patients with anti-Xa level within the therapeutic range.[8] In conclusion, patients with high risk of bleeding receiving LMWH should be identified, and appropriate measures such as close monitoring and dose adjustment should be applied.

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RESPONSE LETTER TO DR. ENRIQUE ANTON

To the Editor: In reply to the letter from Anton et al., we would like to point out the following. We agree that our series had a high risk profile for hemorrhagic events, but these are the standard patients admitted to our department because of cardiovascular disease. Most of our patients receive a combination of low-molecular-weight heparin (LMWH) and antiplatelet drugs if admitted because of acute coronary syndrome. Thus, this profile is frequently found and probably not only in our department. Lately, we are becoming more aggressive in treating elderly patients. As a consequence, we see more complications due to this aggressiveness. In addition, the cases presented are those that had a complication. Thus, it is not a surprise that these are the ones with a higher risk profile.

Alternatively, the designation "spontaneous" is appropriately used to differentiate it from other hematomas that develop after a trauma or an invasive procedure, as mentioned in the Methods part of our article. The reference Anton et al. cite stating that bleeding can occur with a normal anti-Factor-Xa level is only a case report of a 74-year-old man who underwent an invasive procedure.[1] This is not an adequate comparison with our spontaneous hematomas. Creatinine clearance (ClCr) is indeed the most accurate way of measuring renal function, particularly in elderly subjects in whom a "normal" serum creatinine value might represent a significantly reduced ClCr. Unfortunately, as has happened to other authors before, it could not be included in the analysis because of the lack of data for the whole series. The creatinine value reported is the first renal parameter usually available when hospitalizing a patient. Because most patients had a creatinine value of approximately 1 mg/dL, dose adjustment was not performed. It has not been until recently that the Food and Drug Administration has approved revisions to the labeling of enoxaparin sodium injections,[2] specifying that "a dosage adjustment is now recommend for patients with severe renal impairment (ClCr $<$30 mL/min), and no specific dosage adjustment is required in patients with mild or moderate renal impairment." Finally, one of the most important conclusions of our series is to point out again the importance of considering renal function when prescribing LMWH, particularly in the elderly population with a normal creatinine value.

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LOW COMORBIDITY AND MALE SEX IN NONAGENARIAN COMMUNITY-DWELLING PEOPLE ARE ASSOCIATED WITH BETTER FUNCTIONAL AND COGNITIVE ABILITIES: THE NONASANTFELIU STUDY

To the Editor: The nonagenarian population represents an unusual age group at the extreme limits of human life. Nonagenarians are predominantly female (and mostly widows), and an important proportion of them are functionally independent.[1–4] Elderly women are more likely to be disabled than elderly men,[3,4] and functional and cognitive status are worse in nonagenarians with higher comorbidity. The aim of this study was to evaluate the functional and cognitive capacity of a cohort of community-living nonagenarians and to assess the influence of sex and comorbidity on their incapacities.

The NonaSantfeliu study is a population-based study of nonagenarian inhabitants in Sant Feliu de Llobregat (Barcelona, Spain). All 305 inhabitants aged 90 and older were contacted. Sixty-one percent replied (n = 186). Participants did not differ significantly from nonparticipants according to age or sex. Institutionalization (n = 49) was the only exclusion criterion.

A geriatric assessment was conducted, and comorbidity (Charlson Comorbidity Index) and sociodemographic data were evaluated. The Barthel Index (BI) of basic activities of daily living (ADLs) and the Lawton and Brody scale for instrumental ADLs were measured. The Spanish version of the Mini-Mental State Examination (MEC),[5] with a score up to 35 ($\leq$23 indicates cognitive impairment), the short version of the Mini Nutritional Assessment questionnaire (short-MNA),[6] and the Barber test (assesses social risk)[7] were also used. Near visual acuity (Snellen chart) and hearing competence (Whisper test) were evaluated.[8] Information on hypertension, diabetes mellitus, dyslipidemia, heart failure, stroke, ischemic cardiopathy, chronic obstructive pulmonary disease, and chronic drug prescription was collected. Nonincapacitated nonagenarians (successful aging) were considered to be those aged 90 and older scoring 91 or more on the BI and 24 or more on the MEC. They were compared with the rest. Normally distributed continuous variables are reported as means ± standard deviations. Categorical variables are reported as proportions. The Student *t* test, the chi-square or Fisher exact, and multiple logistic regression analysis were performed. $P<.05$ indicated statistical significance

The sample consisted of 99 women (72%) and 38 men; mean age was 93.1 ± 0.7. There were 115 (84%) widowed, 15 (11%) married, and seven (5%) unmarried. Eighteen percent had dementia—25 of the 114 in the unsuccessful aging group. Fifty-six (41%) had a hearing impairment; 51 (37%) had a vision impairment, and 24 had (17.5%) combined sensorial impairment. The mean values of geriatric assessment were Lawton and Brody scale 2.5 ± 2.3, BI 65.3 ± 23.0, MEC 22 ± 11, short-MNA 11.2 ± 2.4, and Barber test 3.0 ± 1.5. The mean Charlson Comorbidity In-

Table 1. Characteristics of the Subjects

Characteristic	Successful Aging (n = 23)	Unsuccessful Aging (n = 114)	*P*-value
Age, mean ± SD	93.1 ± 4.4	93.1 ± 4.5	.86
Female, n (%)	11 (47)	88 (77)	.009
Previous smoker, n (%)	6 (26)	16 (14)	.26
Barthel Index, mean ± SD	96.3 ± 2.2	59.1 ± 27	<.001
Spanish Mini-Mental State Examination score, mean ± SD	31.4 ± 5	20.7 ± 11	<.001
Lawton-Brody index, mean ± SD	5 ± 2.2	2 ± 2	<.001
Mini Nutritional Assessment questionnaire (short form) score, mean ± SD	12. ± 1.1	10.9 ± 2.5	.005
Barber questionnaire, mean ± SD	1.4 ± 0.7	3.3 ± 1.4	<.001
Hearing impairment, n (%)	9 (39)	47 (41)	.96
Decreased visual acuity, n (%)	4 (17)	47 (41)	.03
Combined sensorial impairment n (%)	0	24 (21)	.01
Charlson Comorbidity Index, mean ± SD	0.4 ± 0.9	1.5 ± 1.9	.007
Hypertension, n (%)	12 (52)	69 (60.5)	.57
Diabetes mellitus, n (%)	2 (8.5)	17 (15)	.52
Dyslipidemia, n (%)	2 (8.5)	21 (18.5)	.36
Previous stroke, n (%)	1 (4)	26 (23)	.04
Ischemic heart disease, n (%)	3 (13)	12(12.5)	.71
Chronic obstructive lung disease, n (%)	4 (17)	17 (15)	.74
Heart failure, n (%)	3 (13)	29 (25.5)	.28
Number of drugs taken, mean ± SD	3.4 ± 3	4.2 ± 2.5	.17
More than three drugs, n (%)	10 (43)	66 (58)	.29

SD = standard deviation.

dex was 1.43 ± 1.7. Fifty-nine percent had hypertension, 14% diabetes mellitus, 17% dyslipidemia, 11% ischemic cardiopathy, 25% heart failure, and 15% chronic obstructive lung disease and 20% had suffered a stroke. Patients were taking an average of 4.1 ± 2.4 drugs, and 76 patients (55%) took more than three drugs. The differences between the two groups are displayed in Table 1. Using multiple logistic regression analysis, successfully aging nonagenarians were significantly associated with male sex (odds ratio (OR) = 4.23, 95% confidence interval (CI) = 1.58–11.38; $P = .004$) and with lower comorbidity (OR = 1.94; 95% CI = 1.13–3.35; $P = .01$).

Physical and cognitive dysfunction represent two of the most dreaded states in older people because they can lead to dependency and social isolation. In our study, in the more-successful aging group, a significant predominance of men was found. These results confirm previous data showing greater female incapacity within this age range.[3,4] More than differences in incidence, the higher prevalence of disability in women may explain the greater survival rate of women with severe disability.[3] Global comorbidity, evaluated using the Charlson Comorbidity Index, was higher in the group with worse functional and cognitive capacity. This unsuccessful aging group had a higher prevalence of patients who had previously had a stroke, but this did not attain significance in multivariate analyses. Loss of auditory acuity and sensory deprivation can affect some ADLs.[9] The better-aging group had a lower percentage of visual and combined sensory deficits, not significant in the multivariate analysis.

In the oldest old, several known predictors of mortality, such as sociodemographic factors, smoking, and obesity, have lost importance, but high disability level and poor physical and cognitive performance are useful for predicting mortality.[10]

This study has several limitations. We examined the association between current diseases and disability but did not evaluate previous disability. The small sample size, especially because of the few men included, may suggest some careful ratification to the sex differences found.

In conclusion, male nonagenarians with low comorbidity probably undergo more successful aging than do women or those with high comorbidity.

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MARKED ELEVATION OF THE ST SEGMENT IN CEREBELLAR HEMORRHAGE

To the Editor: Electrocardiographic changes occur most frequently in patients with acute cerebrovascular disease,[1] and the sympathetic nervous system appears to be important in the pathogenesis of these electrocardiographic changes. Excessive sympathetic nervous activity can result from increased intracranial pressure.[2] Hydrocephalus often complicates cerebellar hemorrhage, which increases intracranial pressure, because of mass effects on the fourth ventricle. Electrocardiographic changes with subarachnoid hemorrhage have often been found, but those with cerebral hemorrhage are rare.[3,4] There has not been any previous report of electrocardiogram (ECG) showing marked elevation of the ST segment in a patient with cerebellar hemorrhage.

CASE REPORT

The patient, a 90-year-old female, was brought to our hospital by ambulance November 14, 2003, because of chest

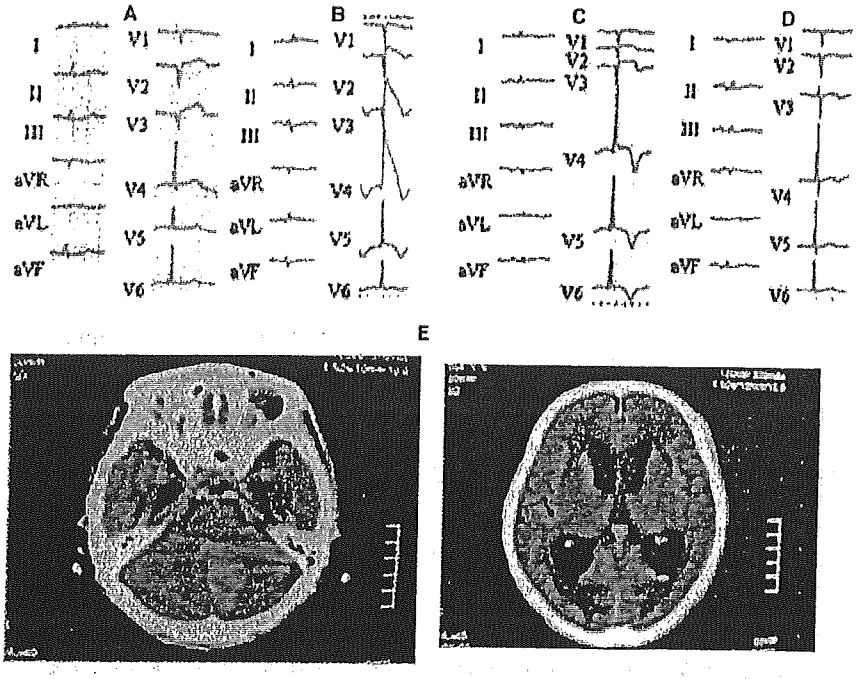

Figure 1. A. Electrocardiography on admission. B. Electrocardiography 1 day after admission. C. Electrocardiography 2 days after admission. D. Electrocardiography 1 month after admission. E. Cranial computed tomography scan 1 day after admission demonstrated cerebellar hemorrhage and hydrocephalus.

pain with nausea and vomiting. She did not have a history of chest pain or other contributory medical history. On admission, she remained completely awake, blood pressure was 173/103 mmHg, and pulse rate was 75 beats/min. Her creatine phosphokinase (CPK) level was 111 IU/mL (normal rang: 43–165IU/L). ECG on admission showed Q waves in V1 and V2 leads (Figure 1A). Transthoracic cardiac ultrasonography showed reduced left ventricular wall motion in the anteroseptal area.

One day after admission, she showed a decreased level of consciousness. Her blood pressure was 155/92 mmHg and pulse rate was 98 beats/min. ECG demonstrated marked elevation of the ST segment in V2, V3, and V4 leads (Figure 1B). Cranial computed tomography (CT) scan demonstrated cerebellar hemorrhage and hydrocephalus (Figure 1E). Two days after admission, cranial CT scan showed improved hydrocephalus, and ECG showed negative T waves in the V4, V5, and V6 leads (Figure 1C). The patient was alert. The maximal CPK level was 237 IU/mL 24 hours after the elevation of the ST segment.

One month after admission, cranial CT scan did not show hydrocephalus. ECG findings normalized except for the negative T waves in the V3 and V4 leads (Figure 1D). Her stay was not complicated by arrhythmia or congestive heart failure. Left ventricular wall motion in the anteroseptal area was reduced.

DISCUSSION

In this case, the patient developed cerebellar hemorrhage on admission, and ECG had not shown elevation of the ST segment. One day after admission, CT demonstrated a mass effect in the fourth ventricle, and ECG showed marked elevation of the ST segment. There has not previously been any reported association between marked elevation of the ST segment and hydrocephalus due to cerebellar hemorrhage.

In this case, ECG showed marked ST segment elevation. ECG changes have been described after various types of cerebrovascular accidents. Most ST segment abnormalities have involved depression of the ST segment or inverted T waves, whereas elevation of the ST segment has been rare.[3,4] ECG abnormalities after cerebrovascular events have been associated with increased intracranial pressure and have not always involved ST segment elevation.[5]

Electrocardiographic changes in this case were similar to those of myocardial ischemia.[6] Transient left ventricular wall motion abnormalities, such as stunned myocardium, have been reported in myocardial injury, triggering conditions such as emotional exposure, physical stress, and cerebrovascular disease.[7] The mechanism of this myocardial injury has been postulated to be multiple vasospastic angina pectoris due to enhanced sympathetic activities. Coronary angiography was not performed in this case because the patient was elderly. In this patient, excessive sympathetic activity, inferred from the pulse rate increase, might have contributed to the triggering of marked elevation of the ST segment. Variant angina pectoris might cause myocardial ischemia, resulting in a transient increase in coronary vasospasm, which might be due to excessive sympathetic nervous activity induced by increased intracranial pressure.

The increased intracranial pressure due to hydrocephalus associated with intracranial hemorrhage might induce electrocardiographic abnormalities and cardiac damage and be associated with severe cardiac arrhythmia and con-

gestive heart failure. Therefore, careful electrocardiographic monitoring might be required after intracranial hemorrhage. In elderly patients, when marked ST elevation is present on ECG, we must differentiate acute cerebrovascular disease.

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NOROVIRUS OUTBREAKS IN NURSING HOMES

To the Editor: Some clinicians may not be familiar with recent recommendations developed by public health officials after experiences controlling norovirus (formerly known as "Norwalk-like viruses") outbreaks on cruise ships. Noroviruses are also a common cause of gastrointestinal outbreaks in nursing homes.[1–3] This illness is known as "stomach flu" or "winter vomiting disease," although it tends to be associated more with diarrhea in older patients.[1] The incubation period ranges from 11 to 48 hours, with disease duration from 12 to 60 hours.[1,4] Infection does not generally appear to confer long-term immunity.[1,5] Norovirus illness typically has an abrupt onset and is characterized by nausea, vomiting, nonbloody diarrhea, and variable systemic symptoms including fatigue, myalgia, headache, chills, and fever. (Residents are often not febrile.)[1,2,4,6] Bismuth subsalicylate has been demonstrated to provide symptomatic treatment and reduce the duration of abdominal cramps and gastrointestinal symptoms in adults in an experimental study.[7] Affected individuals should be considered infectious and isolated/separated for 2 to 3 days after their last symptoms.[8] The disease is usually self-limited but in the frail elderly may be associated with life-threatening dehydration and mortality.[9] If transmission of this illness within a nursing home is suspected, public health officials should be contacted to facilitate diagnostic testing and consult regarding control measures.

Transmission may be person-to-person after contact between stool or vomit and mouth, or may be food-borne.[1,4] Sharing bathrooms is a risk factor for transmission.[6] Affected residents should have a private bathroom or commode. Practitioners may not be aware of transmission via aerosolization, especially during vomiting in a confined space.[4,6,8,10] In one well-documented report, airborne transmission occurred in a restaurant after a single episode of vomiting. Attack rates showed a clear inverse relationship with distance from the vomiter.[4] In other studies, exposure to nearby vomiting (6 feet) or sharing a cabin with someone who vomited in the cabin was a significant risk factor for acquiring gastroenteritis.[6,10] Aerosolization may also occur when caregivers clean toilets, clean up body fluid spills, vacuum carpets, strip linen from beds, or manipulate soiled laundry.[1,9] Therefore, appropriate secretion precautions include contact precautions, including the use of gowns, gloves, and masks, especially if the resident is vomiting or when cleaning areas contaminated with feces or vomit.[1,8,9] Because of the high attack rates that may be seen during norovirus outbreaks, strong consideration should be given to restricting and controlling visitors, interactions between outbreak units and nonoutbreak units, and separating staff.[8]

Clinicians may not be familiar with the fact that the usual quaternary ammonia disinfectants do not provide adequate disinfection.[3,8] Noroviruses are small, nonenveloped ribonucleic acid viruses that are not reliably inactivated by quaternary ammonia compounds.[3] Rather, a fresh 10% bleach solution should be used. Two other products, potassium peroxomonosulfate and parachlorometaxylenol, have demonstrated experimental efficacy against feline caliciviruses.[8,9] Practitioners are advised to consult local public health officials regarding the use of these alternate products. Outbreaks in hotels and on cruise ships have occurred that involve successive cohorts of guests, implying that contamination of the environment may be a factor in transmission.[5,6] Because small numbers of viral particles may be infectious, significantly enhanced environmental cleaning should be emphasized. Some authorities recommend increasing the frequency of cleaning to two times per day, especially for frequently touched objects such as door handles, light switches, faucet handles, and physical therapy equipment.[8] Finally, thorough steam cleaning or disinfection with bleach is recommended for contaminated carpets and upholstery.[5,8,9] In vitro studies with a related feline virus indicate that ethanol fails to completely inactivate the virus; an antiseptic "soap" with friction and running water should provide better disinfection.[3]

Medical directors will need a "case definition" to facilitate staff's ability to track the outbreak. A sensitive and specific case definition is optimal. One definition

to consider: "Acute onset of vomiting or nonbloody diarrhea lasting at least 24 hours that could not be explained by another cause (i.e., medications, pre-existing pattern or disease)."[2]

It is important for physicians to recognize outbreaks of gastrointestinal illness caused by noroviruses and to know that the usual quaternary ammonia disinfectants and alcohol hand gels do not provide optimal antimicrobial activity and that the pathogen may be transmitted by aerosolization, especially during vomiting, requiring the use of masks. Caregivers should avoid mechanical events that may produce aerosolization of body fluids. Practitioners are advised to contact local public health authorities when outbreaks are suspected.

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SONOGRAPHY AND VISUALIZING ROTATOR CUFF INJURIES IN OLDER PEOPLE

To the Editor: A 63-year-old man was seen in June 2004 for complaints of pain in the right shoulder, neck, and low back regions. He denied any trauma or a specific incident to be contributory. Physical examination of the spine was consistent with impaired motion of the cervical and lumbar segments in all directions. Shoulder motions were normal, and resisted tests were negative, but the biceps muscles were suspected to have ruptured bilaterally because of their abnormal configuration. Radiographs of the patient uncovered cervical/lumbar spondylosis with C3-C4 and L5-S1 anterolisthesis and degenerative changes in the shoulder joints. Ultrasonography (US) of the shoulders revealed fluid in the left acromioclavicular joint, absent right supraspinatus tendon and thin subscapularis tendon, and absent bicipital tendons (long head) bilaterally. Because his shoulder functions did not seem to be significantly affected, he was treated with nonsteroidal antiinflammatory drugs and isometric exercises for strengthening the shoulders, neck, and low back.

He was seen again in January 2005 for acute exacerbation of right shoulder pain. He described the pain to have ensued nearly 1 week before when he was doing garden work (cutting roses). He added that he had otherwise been well with the aforementioned treatment. On physical examination, a gross discoloration (yellow-blue) was observed on the anteromedial side of the right arm; shoulder mobility was again normal with negative resisted tests. Considering the place of discoloration and his previous history of bicipital tendon rupture, a likely diagnosis of a new rupture pertaining to the short head of biceps muscle was suspected. Repeat US of the patient depicted right subscapularis tendon rupture in addition to previous US findings. He was treated conservatively.

More than one third of people aged 60 and older suffer significant rotator cuff (RC) disease.[1] The underlying etiology is multifactorial but is often related to the tensile strength of the RC tendon and the amount of force applied. History of an acute traumatic event is common in patients younger than 60, but as the senescent changes of the RC progress, less force is needed to precipitate failure of the tendon. Older patients may present with a gradual onset of shoulder pain, often affecting them at rest and disturbing their sleep, with clinical evidence of a full-thickness RC tear but without a clear history of antecedent trauma.[1] In addition, depending on the size of the tear, some patients may also develop symptoms (e.g., decreased daily activity) after a few years of silent disease course.[2]

Radiographic findings consistent with degeneration (sclerosis, osteophytic spurs, subchondral pseudocysts on the greater tuberosity or the acromion process) correlate with the presence of a tear,[3] but US, magnetic resonance imaging, and arthrography have proven to provide better estimates of the rotator cuff pathology.[4] Nonetheless, imaging findings must be considered in a clinical context and should never be used as the sole basis for a surgical decision, although the critical amount of intact tendon or muscle that is necessary to maintain normal range of motion and strength has not been clarified.

This case implies some interesting points. The patient had bilateral chronic rupture of the biceps tendon and a recent unilateral subscapularis tendon rupture with pain but no functional loss. Isolated rupture of the subscapularis tendon without supraspinatus tendon pathology is rare; moreover, a hematoma would normally be expected to

ensue nearby its insertion. At first glance, the injury seemed to be a biceps rupture, but further sonographical evaluation discovered the pathology. Keeping in mind that age of 65 and older[5] and the concomitance of biceps tendon ruptures, especially in women,[1] have been associated with an inferior postoperative outcome, treating these patients conservatively would not be unfounded. Finally, US seems to be convenient and promising for better diagnosing this group of patients with regard to their commonly seen shoulder problems.

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SUBCORTICAL VASCULAR DISEASE DETECTED WITH COMPUTED TOMOGRAPHY AND 1-YEAR PHYSICAL DECLINE IN HIGH-FUNCTIONING OLDER ADULTS

To the Editor: In their article recently published in the *Journal of the American Geriatrics Society*,[1] Rosano et al. found that subclinical structural brain abnormalities (i.e., ventricular enlargement, white matter hyperintensities, subcortical and basal ganglia small brain infarcts) in high-functioning older adults can increase the risk of developing physical disabilities and declining in motor performances.

Because of the clinical relevance and the prognostic implications of this topic, we decided to investigate the risk of declining motor performance in a similar population using a low-cost neuroimaging tool (computed tomography (CT) of the brain) to detect subcortical vascular disease (SVD, white matter hyperintensities, subcortical and basal ganglia small brain infarcts)

Between January 2003 and January 2004, 349 patients were consecutively admitted to our Rehabilitation and Aged Care Unit after orthopedic surgery (n = 82) or as a

Table 1. Characteristics of 203 Elderly Patients Stratified by Functional Change from Discharge to 12-Month Follow-Up

Variable	Functional Status at 12 Months		
	Improved/Unchanged (n = 104)	Worse (n = 99)	*P*-value*
Age	76.1 ± 5.7	80.3 ± 5.5	<.005
Female, n (%)	84 (80.8)	75 (75.8)	.77
Living alone at home before hospital admission, n (%)	57 (54.8)	57 (57.6)	.77
Body mass index, kg/cm^2, mean ± SD	25.2 ± 4.9	24.4 ± 4.2	.20
Charlson Comorbidity Index, mean ± SD	2.1 ± 1.4	2.8 ± 1.6	.002
Diabetes mellitus, n (%)	15 (14.4)	18 (18.2)	.56
History of coronary heart disease, n (%)	7 (6.7)	11 (11.1)	.32
Mini-Mental State Examination score, mean ± SD (range 0–30)	24.6 ± 3.2	22.7 ± 5.0	.002
Geriatric Depression Scale score, mean ± SD (range 0–15)	5.4 ± 3.5	7.0 ± 3.6	.002
Barthel Index 1 month before hospital admission, mean ± SD (range 0–100)	93.0 ± 8.4	90.1 ± 8.8	.01
Barthel Index at hospital admission, mean ± SD (range 0–100)	77.2 ± 18.9	75.3 ± 20.5	.48
Barthel Index at hospital discharge, mean ± SD (range 0–100)	93.8 ± 6.1	91.8 ± 6.0	.02
Drugs at hospital discharge, n, mean ± SD	5.2 ± 1.5	5.0 ± 1.9	.47
Subcortical vascular disease, mean ± SD	20.3 ± 16.7	26.4 ± 15.9	.009

*Significance using *t* test or chi-square.
SD = standard deviation.

consequence of stroke (n = 25), Parkinson's disease (n = 31), and gait and balance disorders (n = 211). All underwent a multidimensional assessment including sociodemographics (age, sex, living conditions), nutritional and somatic status (body mass index, Charlson Index, number of drugs on admission and at discharge, and presence of diabetes mellitus and ischemic heart disease), cognitive status (Mini-Mental State Examination (MMSE)), affective disorders (Geriatric Depression Scale (GDS)), and functional status (Barthel Index). The Barthel Index from 1 month before admission was compared with the Barthel Indexes at admission and discharge. The presence and severity of cortical, white-matter, and deep subcortical lesions and of leukoariosis were assessed on CT film with a standardized visual rating scale, which has been previously validated and used in elderly patients.[2,3]

Of the 349 patients, 217 (62.2%) had a Barthel Index at discharge greater than 80/100, indicating a high-functioning level. At 12 months, 14 (6.5%) of these subjects had died. For subjects who were still alive, information about two specific items of Barthel Index—12-month transfer and walking abilities—was gathered using phone interviews. A sumscore for these items was created to measure mobility and walking performance at discharge and at 12 months, and the difference between the discharge and 12-month sumscores was computed; patients were therefore stratified in two groups according to change in functional status (difference in sumscore <1 denoted improvement or stability, whereas difference in sumscore ≥ 1 denoted decline). Table 1 shows that SVD ($P=.009$); age ($P<.005$); comorbidity (Charlson Index, $P=.002$); and cognitive (MMSE, $P=.002$), affective (GDS, $P=.002$), and functional status (Barthel Index before admission, $P=.01$, and Barthel Index at discharge, $P=.02$) were significantly different in the two groups.

Our findings support those of Rosano et al. that SVD, in addition to other typical variables of geriatric assessment, is associated with functional decline in high-functioning older patients. Alternatively, they suggest that brain CT may be useful in predicting long-term outcomes and accurate. In rehabilitation, barriers to widespread neuroimaging use include costs and availability of diagnostic tools.[4] From this perspective, CT may be viewed as a valid option.

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SUBJECTIVE ESTIMATES OF COGNITIVE IMPAIRMENT IN OLDER SURGICAL PATIENTS: IMPLICATIONS FOR GIVING INFORMED CONSENT

To the Editor: Assessing cognitive function in older patients is of prime importance if consent for invasive procedures is being sought. Although cognitive impairment is prevalent in the older inpatient population, health professionals tend to underrecognize it.[1] One important ethical and legal consequence of cognitive impairment may be a reduction in the capacity to give consent.

Objective rating scales such as the Abbreviated Mental Test (AMT) are often used to screen for cognitive impairment. Although cognitive impairment does not preclude the capacity to give consent in a particular situation, recognizing impairment should raise the possibility that capacity needs to be specifically assessed.[2] The UK Department of Health guidelines state that this evaluation of capacity is

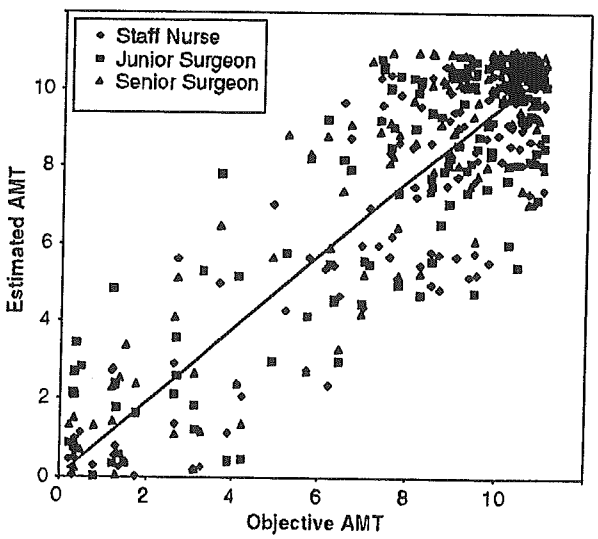

Figure 1. Scatterplot of actual Abbreviated Mental Test (AMT) score versus predicted AMT score. (Diagonal line indicates perfect agreement; random noise was added to the data before plotting to avoid points being plotted on top of each other.)

essential before an invasive procedure. In England, there is a standardized "Consent Form 1" used as evidence of a patient's consent. A separate "Consent Form 4" exists when an adult patient is determined not to have the capacity to give or withhold consent.[3]

This report examines how accurately staff on surgical wards can detect cognitive impairment if the formal assessment of capacity is not undertaken and how these subjective judgments may influence the process of obtaining consent.

METHODS

One hundred fifty-one subjects aged 65 and older consecutively admitted to general and orthopedic surgical wards were approached to participate (age range 65–98, mean 78, median 80). Twelve patients whose cognitive function had already been objectively assessed using an AMT (or other test) were excluded, leaving 139.

Three groups of health professionals involved in the care of each patient (staff nurse, junior surgeon, senior surgeon) were asked to subjectively estimate the cognitive function of their patient based on routine clinical contact. Professionals were given copies of the AMT questions on which to base their estimations. Subjective estimates were blinded. A single rater (DD) then objectively evaluated the cognitive function of each participant using performance on the AMT. A score of 0 to 7 was taken to indicate cognitive impairment. All estimates and evaluations took place on the same working day. The chairperson of the local research ethics committee approved the protocol. Statistical analyses were conducted using Stata (StataCorp., College Station, TX).

RESULTS

Subjective estimates were plotted against objective AMT scores to demonstrate the level of agreement between each evaluation (Figure 1). Weighted kappa values quantify this as: staff nurses 0.62, junior surgeons 0.61, and senior surgeons 0.66. Overall, no staff group was significantly better at estimating the cognitive function of patients.

Forty-eight of 139 (35%) participants had an AMT score between 0 and 7. Of these, staff nurses incorrectly labeled eight (17%) patients as cognitively intact. Of the 59 patients judged by nurses to have cognitive impairment, 19 (32%) had AMT scores of 8 or more. Similarly, junior surgeons incorrectly labeled 11 of 48 (23%) as cognitively intact and 15 of 52 (29%) cognitively impaired. Senior surgeons judged 13 of 48 (27%) and 10 of 45 (22%) incorrectly as cognitively intact and impaired, respectively. For those participating, 68 procedures were performed, with consent being documented using Consent Form 1 in 64 cases. Of these, 52 (81%) had AMT scores between 8 and 10. Based on AMT score, 12 (19%) procedures were performed in patients whose cognitive impairment had not been determined and so may have lacked capacity. In these cases, Consent Form 4 may have been more appropriate.

DISCUSSION

This study demonstrates that guessing at a patient's cognitive function commonly leads to error, and this can result in procedures being undertaken without proper legally valid consent.

Across the full range of cognitive function, comparison of actual and estimated AMT scores indicates good levels of agreement, but the estimates are less accurate when only patients with actual AMT scores of 0 to 7 are compared (staff nurses 0.56, junior surgeons 0.50, senior surgeons 0.52). Furthermore, for patients with AMT scores of 3 to 7, staff predictions were poor (staff nurses 0.30, junior surgeons 0.25, senior surgeons 0.28). Although staff found it easier to recognize extremes of cognitive functioning, when a patient's degree of cognitive impairment was intermediate, estimates were only slightly better than that expected by chance. This is in keeping with previous findings in medical patients.[4]

Any surgeon obtaining consent is at risk of misjudging a patient's capacity if cognitive function is not specifically evaluated. This possibility is highest when moderate impairment is present and may result in patients undergoing procedures without their capacity to consent being properly assessed.

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ANTICOAGULANT USE FOR ATRIAL FIBRILLATION IN OLDER PEOPLE

To the Editor: We read with interest the Brophy et al.[1] article, published in the July issue, on anticoagulant use for atrial fibrillation (AF) in older people.

The attitude of physicians toward anticoagulation use in older people over the past decade is an interesting study.[2] In a 1989 survey based in New Hampshire (with a response rate of 49%), Chang et al.[3] demonstrated that 34.6% of internists would elect to use warfarin in a 73-year-old man with new-onset AF. In a study based in New York, Kutner et al.,[4] in 1991, found that warfarin was used in only 18.3% of subjects aged 65 and older with AF of any cause. By

1995, McCrory,[2] in a vignette-based questionnaire survey that used a national sample with a response rate of 38%, showed that 63% of the respondents would choose to use anticoagulation in subjects aged 75 and older with AF and left atrial enlargement, but there is a difference between physicians' attitude and practice (based on chart reviews) on the use of anticoagulants (51% vs 24%).[5] Dr. Brophy's article confirms that advancing age is a deterrent to the use of anticoagulation in Department of Veterans Affairs (VA) subjects.

There are a few critiques of the article. Both the cohorts had variable follow-up that was dependent on the time of encounter with the MUSE database and the number of encounters in the VA clinical database. In addition, the risk factor identification appeared to select incidence as well as prevalence of disease. The exclusion of 747 subjects because of the presence of AF on electrocardiogram but not in the *International Classification of Diseases, Ninth Revision*, codes is of concern. It points to the problems with database analysis, and the sensitivity analysis with the addition of this group to the anticoagulant-free group would dramatically alter the rate of anticoagulation. The use of any prescription of warfarin as a marker of anticoagulation leaves the question of intensity and adequacy of the anticoagulation unanswered. The database fails to capture the fact that age may be a marker of multiple comorbidities and physicians' perception of risks and benefits. The proportional increase in rates of anticoagulation in this study as the numbers of risk factors increases in both cohorts despite advancing age is a hopeful sign.

In conclusion, we believe that this study has several limitations and results could change with a different study. Further in-depth studies examining risks and benefits of anticoagulation and barriers to anticoagulant use will help in reducing reluctance to use them in older people with AF.

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RESPONSE LETTER TO DR. PATEL

To the Editor: Patel raises a number of concerns about the design of our study. Using administrative and patient-care databases, we identified subjects with atrial fibrillation (AF), identified risk factors (comorbidities) for stroke, and found that advancing age was a deterrent to warfarin administration for stroke prevention. The case definition of AF required both a healthcare encounter with a diagnostic code (International Classification of Diseases, Ninth Revision (ICD-9)) for AF as well as a recorded electrocardiogram (EKG) tracing for this arrhythmia. A medical record–based validation substudy demonstrated 97% accuracy of the diagnosis in the cohort. Patel noted that 747 potential subjects were excluded because ICD-9 diagnostic data did not confirm the EKG finding and suggest that inclusion of these individuals might have "dramatically" changed the results. Because a validation substudy of these excluded subjects confirmed AF in only 26% of the sample (unpublished data), we felt it prudent to exclude them from further analyses.

Patel makes note of potential weaknesses in our method of ascertaining comorbidities and further point out that the "use of any prescription of warfarin as a marker of anticoagulation leaves the question of intensity and adequacy of the anticoagulation unanswered." We agree with these concerns and note only that the available data limit the methods used and the questions that can be addressed in a nonexperimental (database) study. Such studies are rarely comprehensive or definitive but rather inform in an exploratory or confirmatory capacity. Despite this, we feel that our study clearly demonstrates that, in clinical practice, age is a deterrent to anticoagulant use for stroke prevention in AF.

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Brain and CNS

Nocturnal Hypoxia Is Associated With Silent Cerebrovascular Disease in a High-Risk Japanese Community-Dwelling Population

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Background: Sleep-disordered breathing (SDB) is recognized as a risk factor for cerebrovascular disease. The objective of this study was to investigate the relationship between nocturnal hypoxia and silent cerebral infarct (SCI) in the general population.

Methods: In the 2001 annual health check in Nishiarita, Japan, 170 individuals at high risk were screened who met more than three of the following criteria: high blood pressure, hypercholesterolemia, left ventricular hypertrophy by electrocardiography, hemoglobinA_1c >6.5%, proteinuria, central obesity, heavy smoking habit, heavy drinking, and family history of stroke. Overnight pulse oximetry, brain magnetic resonance imaging, and carotid/cardiac ultrasonography were performed in 146 (mean age 67.4 ± 9.0 years) of the 170 individuals in whom pulse oximetry was successfully performed.

Results: Subjects were classified into a nocturnal hypoxia group (n = 36) and a nonhypoxia group (n = 110) based on a 3% oxygen desaturation index (ODI) 5.6 times per hour during sleep (highest quartile) by pulse oximetry. The presence of silent cerebral infarct (SCI) (57% v 35%, P = .03) was significantly higher in the hypoxia group than in the nonhypoxia group. The number of SCI was positively correlated with age (r = 0.23, P < .01), systolic blood pressure (r = 0.196, P < .05), and 3% ODI (r = 0.318, P < .001). Even after adjustment for confounding factors using logistic regression analysis, nocturnal hypoxia (odds ratio = 2.2, 95% confidence interval = 1.10 to 5.30, P = .026) as well as systolic blood pressure and age (10-year increase: odds ratio = 1.22, 95% confidence interval 1.00 to 1.48, P = .048) were independently associated with SCI in the study subjects.

Conclusions: Based on the study results, SDB assessed by overnight pulse oximetry was associated with silent cerebral disease in a high-risk, community-dwelling Japanese population. Am J Hypertens 2005;18: 1489–1495 © 2005 American Journal of Hypertension, Ltd.

Key Words: Nocturnal hypoxia, silent cerebral infarct, overnight pulse oximetry, community screening.

Sleep-disordered breathing (SDB) is an important health problem affecting 2% to 4% of the middle-aged population in a random sample of state employees in Wisconsin.[1] This disorder has been reported to be associated with hypertension, cardiovascular diseases, future stroke,[2,3] and greater morbidity.[1] The disorder is composed of habitual snoring, increased upper airway resistance syndrome, periodic breathing, and sleep apnea disorder. The type, severity, and therapeutic indication of SDB can be diagnosed by polysomnography as a "gold standard" diagnostic tool; but it requires an overnight stay at a sleep laboratory, which is somewhat complicated, troublesome, and not always useful for community screening of SDB. An overnight pulse oximetry is helpful for screening of SDB.[4–6] Early detection of silent cerebral infarct (SCI) is important because SCI is associated with higher rates of mortality and subsequent clinical cerebral infarction.[7–9] It has been reported that SCI is associated with many traditionally recognized cerebrovascular risk factors in-

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