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Prognostic Implications of Swallowing Ability in Elderly Patients After Initial Recovery From Stroke

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Background. It remains unclear how swallowing assessment can help clinicians to predict the risk for pneumonia in elderly persons after ischemic stroke. A prospective case-control study was conducted to evaluate the prognostic utility of swallowing ability assessments.

Methods. Participants were 136 elderly persons who had an acute ischemic stroke 3–12 months previously. They were separated into four groups based on their history of repeated episodes of pneumonia in combination with swallowing ability: Group 1 had neither repeated pneumonia nor swallowing abnormality ($n = 69$); group 2 had repeated pneumonia but no swallowing abnormality ($n = 0$); group 3 had swallowing abnormality but no repeated pneumonia ($n = 54$); and group 4 had both swallowing abnormality and repeated pneumonia ($n = 13$). The follow-up period was as long as 2.2 years. Outcomes and causes of death were compared among the groups.

Results. During the study, the overall mortality rate was higher in group 3 (24 deaths, 44.4%) and group 4 (9 deaths, 69.2%) than in group 1 (3 deaths, 4.3%, both $p < .05$). The annual mortality rate from pneumonia was also significantly higher in group 3 (21.2%) and group 4 (38.2%) than in group 1 (0.8%, $p < .0001$). The odds ratio for patients who subsequently died of pneumonia was 46.8 between groups 1 and 3.

Conclusions. The high sensitivity (.96) and specificity (.68) of swallowing ability indicate that the method is useful for identifying those persons at greatest risk for pneumonia and death after ischemic stroke.

OUTCOMES for persons who survive acute ischemic stroke depend largely on whether subsequent vascular disease or pneumonia develops. We have previously studied outcomes among elderly persons after initial ischemic stroke and reported 5-year mortality rates of approximately 20% from aspiration pneumonia (1). In addition to adversely affecting outcomes in persons with ischemic stroke, pneumonia can also compromise activities of daily living and is associated with the development of dementia (2). Prevention of pneumonia should therefore be an important goal in medical care. Because the risk for aspiration pneumonia is linked to dysphagia (3,4), accurate evaluation of swallowing ability is a prerequisite for the care of persons after ischemic stroke. Many techniques have been developed to assess swallowing ability (5–16), but the method described by Smithard and colleagues (5) is straightforward and can be performed at the bedside. However, the proportion of patients with an identifiable risk for dysphagia remains unclear. In the current study, we used the Smithard method to evaluate dysphagia in patients after ischemic stroke, and we considered the relationship between dysphagia status and outcome.

Methods

We conducted this prospective study from June 1999 through September 1999 at an urban, long-term rehabilitation ward. We performed the study in accordance with the Declaration of Helsinki (17). All patients gave their informed consent to undergo the water drinking test. The study group consisted of 136 elderly patients aged 60 years or older, for whom 3–12 months had elapsed since their last ischemic stroke, as verified on brain computed tomography.

All patients had some degree of motor disturbance and had been admitted to the hospital for rehabilitation. We excluded patients who were already receiving parenteral nutrition or had a gastrostomy tube. However, we did include patients treated in this manner after the swallowing assessment in the study. We separated patients into four groups based on their history of repeated episodes of pneumonia in combination with swallowing ability, which was evaluated according to the method described by Smithard and colleagues (5): Group 1 had neither repeated episodes of pneumonia nor swallowing abnormality ($n = 69$); group 2 had repeated pneumonia but no swallowing abnormality ($n = 0$); group 3 had swallowing abnormality but no repeated pneumonia ($n = 54$); and group 4 had both swallowing abnormality and repeated pneumonia ($n = 13$). In this study, we defined repeated episodes of pneumonia as a history of more than two episodes of pneumonia between the time of initial cerebral infarction and enrollment. We defined swallowing abnormality as any abnormality of swallowing during study stages 1, 2, or both. We omitted group 2 from analyses because all patients with repeated episodes of pneumonia displayed swallowing abnormality, and thus not a single patient belonged in this group.

We evaluated swallowing ability in the afternoon, with the patient in a sitting position (if the patient's head or back were unstable, the patient sat in bed with the back inclined at

Table 1. Results of Bedside Swallowing Assessment

Positive Findings	Incidence (%) of Abnormality
Stage 1: Give a teaspoon (5 mL) of water 3 times	
No. of patients at stage 1 (abnormal/total)	40/136
1) Dribbles water	21 (52.5)
2) Laryngeal movement on attempted swallow	3 (7.5)
3) Repeated movements felt	34 (80.5)
4) Cough on swallowing	18 (40.5)
5) Stridor on swallowing	33 (80.3)
6) Laryngeal function after swallowing	34 (80.5)
Stage 2: If the swallow is normal in stage 1 (2 of 3 attempts), try 60 mL of water in a beaker	
No. of patients at stage 2 (abnormal/total)	27/96
7) Unable to finish	13 (48.1)
8) Cough during or after swallowing	22 (81.5)
9) Stridor during or after swallowing	17 (63.0)
10) Laryngeal function after swallowing	26 (96.3)

60° and the neck in anterior flexion). We enrolled patients with impaired consciousness only if they were drowsy but rousable. To evaluate swallowing ability, the patient was given 5 ml of water in a spoon three times (stage 1), followed by 60 ml of water in a cup (stage 2). In stage 2 of the test, the patient had to drink the water (60 ml) within 1 minute, although any number of sips was allowed. Swallowing was clearly abnormal in stage 1 of the test in 40 patients, and therefore testing did not proceed to stage 2 for them (Table 1). Among the remaining 96 patients who proceeded to stage 2, swallowing was abnormal in 27.

We registered eligible patients after evaluation and observed them for as long as 2.2 years. We reevaluated patients on return visits to the hospital or on the basis of medical records or telephone interviews. We observed 96 survivors until the end of the study. Among the other 40 patients, we terminated the study because of death in 36 patients and loss to follow-up after discharge in 4. Thirty-two of the 36 deaths occurred in the hospital. Time and cause of death in the 4 patients lost to follow-up were eventually determined from death certificates. All episodes of pneumonia that required admission for treatment and all patients who received parenteral nutrition or a gastrostomy tube were closely documented. In the follow-up period, we based the diagnosis of aspiration pneumonia principally on clinical findings of a rapid increase in purulent sputum that displayed mixed infection, including anaerobes on bacteriologic examination, and findings on chest radiography showing infiltration shadows in the lower lung fields (18,19).

We recorded the following clinical characteristics of the patients: interval after first stroke, history of pneumonia after first stroke, main neurologic signs and symptoms, risk factors, main findings on computed tomography scans, activities of daily living status, and severity of dementia.

We defined risk factors as hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation. We considered hypertension and diabetes mellitus to be present in patients who were receiving some type of pharmacotherapy or dietetic therapy to manage these diseases. We defined hyperlipidemia as a total serum cholesterol concentration of 220 mg/dl or more at the time of registration. Patients already receiving lipid-lowering agents were also considered to have hyperlipidemia. The presence of atrial fibrillation was confirmed electrocardiographically.

We assessed activities of daily living status according to the Rankin disability scale (20) and classified them, based on the patients' ability to move and walk, as "independent" (Rankin scale, 0–3), "partially dependent" (Rankin scale 4, unable to walk without assistance), or "totally dependent" (Rankin scale 5, bedridden). The presence and severity of dementia were evaluated according to the Clinical Dementia Rating (CDR) score (21). The severity of dementia was classified as "none" (CDR = 0 or 0.5), "mild" (CDR = 1), "moderate" (CDR = 2), or "severe" (CDR = 3).

Statistical Methods

We evaluated differences between groups using analysis of variance, the Kruskal–Wallis test, and Fisher's exact probability test. We analyzed survival using the Kaplan–Meier method, the log-rank test, and StatView software version 5.0 (SAS Institute, Cary, NC). We considered probability values less than .05 to be significant.

Results

Evaluation of Dysphagia

Swallowing was abnormal in 40 patients at stage 1 of testing. The most common abnormalities were repeated movements, coughing on swallowing, and abnormal laryngeal function after swallowing (Table 1). Nearly all of the 27 patients with abnormal results in stage 2 testing had abnormal laryngeal function after swallowing.

Clinical Characteristics

The three groups displayed no differences in age and sex ratio (Table 2). The interval from first stroke until testing varied considerably, but there was no statistical difference in the interval among the groups. Frequencies of hypertension, diabetes, and atrial fibrillation did not differ among the groups. However, the frequency of hyperlipidemia was lower in groups 3 and 4 ($p < .05$). The proportions of patients who required assistance to perform activities of daily living or who had severe dementia were significantly greater in groups 3 and 4 ($p < .05$). Many patients in group 4 were lethargic or had poor head and trunk control or abnormal movement of the lips, palate, larynx, or tongue. Bilateral hemispheric infarcts were frequently seen in groups 3 and 4.

Outcomes

Survival and mortality rates.—During follow-up, 3 deaths occurred in group 1, 24 in group 3, and 9 in group 4. Annual mortality rates were significantly higher in group 3 (29.7%) and group 4 (49.2%) than in group 1 (2.2%, Table 3).

Annual mortality rate related to aspiration pneumonia.—Aspiration pneumonia was considered the cause of death in 1 patient in group 1, in 22 patients in group 3, and in 7 patients in group 4. The patient who died of aspiration pneumonia in

Table 2. Clinical Characteristics of Each Group

Characteristic	Group 1	Group 3	Group 4
n	69	54	13
Mean age, y (range)	75.6 (60–90)	77.9 (60–92)	76.8 (64–84)
Male (%)	39 (56.5)	25 (46.3)	8 (61.5)
Median interval after first stroke, y (range)	1.1 (0.3–23.3)	2.4 (0.4–25.5)	2.5 (0.5–23.5)
Repeated pneumonia after first stroke (%)	0 (0)	0 (0)	13 (100.0)*†
Risk factors (%)			
Hypertension	49 (71.0)	28 (51.9)	9 (69.2)
Diabetes	17 (24.6)	15 (27.8)	3 (23.1)
Hyperlipidemia	15 (21.7)	4 (7.4)*	0 (0)
Atrial fibrillation	8 (11.6)	7 (13.0)	2 (15.4)
ADL status			
Partially/Totally dependent	29/7	15/36*	2/10*
Dementia			
CDR = 1/2/3	11/5/1	13/9/12*	0/3/3*
Disturbed consciousness (%)	0 (0)	6 (11.1)*	7 (53.8)*†
CT findings			
Bilateral hemispheric infarcts (%)	19 (27.5)	32 (59.3)	8 (61.5)*

*$p < .05$ vs Group 1, †$p < .05$ vs Group 3 (analysis of variance, Fisher's exact probability test, nonparametric test).

group 1 had Wallenberg's syndrome, and dysphagia developed after relapse. Annual mortality rates from aspiration pneumonia were significantly higher in group 3 (27.2%) and group 4 (38.2%) than in group 1 (0.8%) (log-rank test: $c2 = 38.8$, $Df = 2$, $p < .0001$; Figure 1).

Episodes of pneumonia during follow-up.—During the follow-up period, aspiration pneumonia developed at least once in 4 patients in group 1, in 36 patients in group 3, and in 10 patients in group 4. Aspiration pneumonia led to death in 30 of these patients.

Table 3. Outcome in Each Group

Characteristic	Group 1	Group 3	Group 4
n	69	54	13
Observation period, y	0.6–2.2	0.1–2.2	0.1–2.2
No. of deaths (%)	3 (4.3)	24 (44.4)*	9 (69.2)*
Annual death rate, %	2.2	29.7*	49.2*
Cause of death			
Pneumonia	1 case	22 cases	7 cases
Myocardial infarction	1 case	2 cases	0 case
Malignancy	1 case	0 case	0 case
Chronic heart failure	0 case	3 cases	0 case
Chronic renal failure	0 case	1 case	0 case
Dehydration	0 case	2 cases	1 case
GI bleeding	0 case	0 case	1 case
DIC, sepsis	0 case	0 case	2 cases
Overlapping		(6 cases)	(2 cases)
No. of stroke recurrence	9 cases	6 cases	0 case
No. of pneumonia (%)	4 (5.8)	36 (66.7)*	10 (76.9)*
Annual death rate due to pneumonia, %	0.8	27.2*	38.2*
No. of PEG after assessment	0 case	24 cases	13 cases

*$p < .05$ vs Group 1 (Fisher's exact probability test, log-rank test).

GI bleeding = gastrointestinal bleeding; DIC = disseminated intravascular coagulopathy; PEG = percutaneus endoscopic gastrostomy.

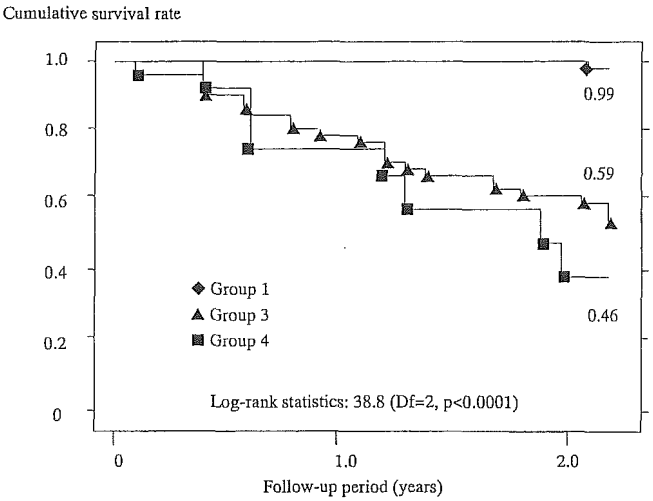

Figure 1. Kaplan–Meier survival curves for each group based on deaths due to pneumonia.

Gastrostomy.—During the follow-up period, 24 patients in group 3 and all 13 patients in group 4 received a gastrostomy tubes. Sixteen of these patients died as a result of pneumonia.

Utility of swallowing assessment for screening.—Among the 123 patients in groups 1 and 3, 23 died of aspiration pneumonia, and 22 of these patients displayed positive results on swallowing assessment (sensitivity, 0.96; Table 4). Of the 100 patients who did not die of pneumonia, 68 had negative results on swallowing assessment (specificity, 0.68). Thirteen of the 23 patients who died of aspiration pneumonia had a history of repeated pneumonia after first stroke (sensitivity, 0.57). Of the 100 patients who did not die of pneumonia, 80 had no history of repeated pneumonia (specificity, 0.80; Table 5).

Discussion

Stroke is the most common disease underlying aspiration pneumonia (18). The mortality rate from aspiration pneumonia is particularly high during the acute phase of stroke (5–9,22). In elderly patients in the chronic phase of ischemic stroke, the risk for death from aspiration pneumonia remains high (10,23). Because dysphagia

Table 4. Sensitivity and Specificity of Swallowing Assessment Test for Identifying Patients at Risk for Subsequent Fatal Pneumonia

	Death Due to Pneumonia		
Swallowing Assessment Test	(+)	(−)	Total
Positive (abnormal)	22	32	54
Negative (normal)	1	68	69
	23	100	123

Odds ratio: 46.8 ($p < .001$)
95% confidence interval, 637.4–3.4
Sensitivity: 22/23 (0.96)
Specificity: 68/100 (0.68)

Table 5. Sensitivity and Specificity of Past History of Pneumonia for Identifying Patients at Risk for Subsequent Fatal Pneumonia

	Death Due to Pneumonia		
Past History of Repeated Pneumonia	(+)	(−)	Total
Present	13	20	33
Absent	10	80	90
	23	100	123

Odds ratio: 5.2 ($p < .001$)
95% confidence interval: 17.7–1.5
Sensitivity: 13/23 (0.57)
Specificity: 80/100 (0.80)

influences outcomes in elderly persons after stroke, straightforward techniques that can accurately evaluate swallowing ability are needed. Various techniques have been developed (5–16), although most screening tests for dysphagia evaluate the ability to swallow water. However, some tests fail to identify mild dysphagia or subclinical aspiration (24,25). To overcome the problems of conventional methods, Smithard and colleagues (5) developed a bedside test to assess swallowing ability. This test consists of two stages, can be performed easily at the bedside, and evaluates swallowing ability at multiple time points. We wanted to determine whether this method was useful for diagnosing dysphagia and predicting outcomes in patients with ischemic stroke.

An important feature of this method is inclusion of a pretest evaluation of laryngeal function, palate movement, gag reflex, and voluntary cough, in addition to level of consciousness and control of the head and trunk. Speech, the ability to repeatedly swallow saliva, and voluntary cough also can be assessed as baseline values for bedside swallowing assessments. When our patients performed water-swallowing tests after such evaluations, we observed high incidences of repeated movements, stridor on swallowing, and abnormal laryngeal function after swallowing. Repeated movements refer to laryngeal movement two or more times on attempts to swallow 5 ml of water. Such repeated movements suggest problems in the oral or laryngeal phases of swallowing (5,6). Stridor on swallowing and abnormal laryngeal function after swallowing suggest decreased laryngeal perception or swallowing reflex, or the presence of aspiration (11,26).

Because repeated episodes of pneumonia were probably caused by aspiration, we excluded data from group 4 when we evaluated the utility of the Smithard method for risk screening. We followed groups 1 and 3 for as long as 2.2 years (average follow-up, 1.7 years), and the accuracy for predicting the risk for death from pneumonia based on the Smithard method was 0.65 (sensitivity, 0.96; specificity, 0.68). In contrast, accuracy for predicting risk for death from pneumonia based on the presence or absence of a history of pneumonia was 0.46 (sensitivity, 0.57; specificity, 0.80). These results suggest that this method is useful for identifying patients with a history of ischemic stroke who are at increased risk for aspiration pneumonia (odds ratio, 46.8).

In addition, the mortality rate from aspiration pneumonia increased at a similar pace in groups 3 and 4. We found no difference in the mortality rate from aspiration pneumonia in groups 3 and 4. Perhaps this lack of difference was related to the fact that many patients in group 3 and all patients in group 4 received gastrostomy tubes after evaluation for dysphagia. Despite this procedure, however, outcomes based on annual mortality rates in groups 3 and 4 were poorer than in group 1. One of the reasons for the poor outcomes would be gastroesophageal reflux phenomenon and oral hygiene, so meticulous attention must be focused on food processing and oral hygiene care (27).

These findings indicate that the Smithard method is helpful for predicting the risk for aspiration pneumonia in patients with ischemic stroke. The study by Smithard and colleagues (5) of outcomes in patients with acute stroke who had dysphagia on bedside swallowing assessment and were followed for 6 months showed high rates of pneumonia, poor nutritional status, and mortality (5). Furthermore, the diagnostic accuracy of the bedside swallowing assessment to detect dysphagia seemed similar to that of videofluoroscopy, the most accurate diagnostic procedure available, based on a comparison of diagnostic accuracy between the two methods (5). In the current study, we show the utility of the bedside swallowing assessment as a screening procedure for dysphagia. In addition to the validity, the convenience of bedside assessment, the use of water volumes, and evaluation variables similar to those of other water-swallowing tests (7,8) further enhance the value of this technique as a screening evaluation for dysphagia. Patients who display even one abnormal finding according to the Smithard method should be followed carefully for aspiration pneumonia. After ischemic stroke, patients should be evaluated carefully and retested at regular intervals, because the results of the bedside swallowing assessment may become positive during follow-up.

Study Limitations

We evaluated swallowing ability 3–12 months after the last acute ischemic stroke, regardless of recurrence or the interval after the first stroke. The interval from the first stroke to the time of testing, therefore, varied considerably. This variation in interval between the first stroke and testing was probably related to the incidence of pneumonia or cerebrovascular diseases, perhaps indicating selection bias. Groups 3 and 4 showed a high incidence of bilateral hemispheric infarction, suggesting that these groups may have had frequent recurrence of ischemic stroke during an extended period, or that stroke may have occurred after the development of unrecognized lesions. This was corroborated by the high incidences of impaired activities of daily living and disturbed consciousness in groups 3 and 4. Background differences in the presence of disturbed consciousness and dementia between the groups could introduce bias in the study and influence prognosis. Furthermore, it is unclear whether episodes of aspiration pneumonia during follow-up were caused by aspiration during meals or during sleep (24,25). Finally, the diagnosis of pneumonia is often attributed to aspiration pneumonia, particularly in patients after stroke, because the diagnosis apparently depends on clinical findings (18,19).

Conclusion

Our results indicate that the bedside swallowing assessment in elderly patients after initial recovery from stroke is useful for identifying those at greatest risk for pneumonia and death.

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ORIGINAL ARTICLE

Platelet aggregation is significantly associated with cardiovascular mortality in elderly patients

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Background: The relationship between cardiovascular mortality and platelet function in elderly patients remains unclear.

Methods: The outcomes for 347 consecutive patients aged 60 or older (mean age 77.5 years; 161 men and 186 women) who were treated without antiplatelet drugs on registration, were retrospectively studied after platelet aggregatability tests. The grading curve (GC) type, as an index of platelet aggregatability, was determined with an aggregometer and adenosine-5′-diphosphate as an agonist. Patients were classified into three groups according to GC type: Group I with suppressed aggregation (n = 40); Group II, normal aggregation (n = 208); and Group III, increased aggregation (n = 99). The mean follow-up was 3.9 years.

Results: There were three deaths in Group I, 33 in Group II, and 30 in Group III. The mean annual mortality rate was 2.1% in Group I, 4.0% in Group II and 7.5% in Group III. Although the most common cause of death was pneumonia in all three groups, the annual mortality rates due to vascular events were 0.7% in Group I, 0.6% in Group II and 4.2% in Group III. Cox proportional hazards models for vascular death yielded a hazard ratio of 1.5 in the increased GC type.

Conclusion: These findings indicated that elderly patients with accelerated aggregation had higher mortality rates due to vascular events. Therefore, accelerated aggregation in the elderly suggested not only the progress of arteriosclerosis, but indications of antiplatelet therapy to prevent vascular events.

Keywords: aging, cause of death, outcome, platelet function, vascular events.

Introduction

Platelet aggregatability increases with age as vascular lesions progress in the elderly.[1–3] Increased platelet aggregatability therefore suggests that thrombotic events might occur in the future, and the circulatory disturbance of the organs might influence the prognosis. However, no reports have dealt with the prognosis of the elderly from the aspect of platelet aggregatability. For this reason, neither a universally accepted quantitative test of platelet aggregatability nor the reproducibility of platelet aggregatability tests have been established. In addition, it has also not yet been clarified whether data obtained regarding platelet aggregatability reflects subsequent platelet function or not. Recently, the grading curve (GC) type, which is obtained from platelet aggregatability curves induced by four different concentrations of adenosine-5′-diphosphate (ADP) based on Born's turbidimetric method,[3,4] has widely been used to evaluate platelet aggregatability semiquantitatively.[1,2,5,6] Therefore, we used this method to study the relationship between platelet aggregatability and

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long-term prognosis of the elderly, as well as the reproducibility of platelet aggregatability.

Subject and methods

Patients

A total of 347 consecutive outpatients aged 60 or older, who had a variety of diseases but had not received antiplatelet therapy, were enrolled in this study, retrospectively in December 2000. They consisted of 161 men and 186 women with a mean age of 77.0 ± 7.6 years. Exclusion criteria included patients with acute illness, blood dyscrasia, severe liver or kidney disease, malignant tumors and severe carotid artery stenosis. A platelet aggregatability test using the GC type was performed. Subsequently, patients were divided into three groups according to GC type: Group I with a GC type of –2 or –1 (suppressed platelet function: $n = 40$); Group II with a GC type of 0 or +1 (normal platelet function: $n = 208$); and Group III with a GC type of +2 or +3 (accelerated platelet function: $n = 99$). After a brain computed tomography (CT) and the assessment of vascular risks described below were performed, patients were followed up for 2–6 years (average: 3.9 years). This study was performed in accordance with the Helsinki Declaration of 1975 as revised in 1983.

There were 80 cases with stroke of chronic phase (including seven cases with cerebral hemorrhage and two cases with cardioembolic stroke), 12 cases with transient ischemic attack, 15 cases with vascular dementia, 14 cases with ischemic heart disease, 11 cases with peripheral artery occlusive disease, 77 cases with vertigo due to circulatory insufficiency in the vertebrobasilar artery territory, 14 cases with Alzheimer's disease, 15 cases with Parkinson's disease and 109 cases with some vascular risk factors alone. Patients were also stratified into three clinical stages on the basis of circulatory disturbance: Stage I, showing no circulatory disturbance in any organ ($n = 139$); Stage II, showing circulatory disturbance without any thrombotic process such as vertebrobasilar insufficiency or cerebral hemorrhage ($n = 84$); and Stage III, in which circulatory disturbance due to thrombosis, such as nonembolic cerebral infarction, transient ischemic attack, ischemic heart disease, peripheral artery occlusive disease ($n = 124$), was apparently seen.

Platelet aggregation test

Fasting blood was collected with a 21-gauge needle from the antecubital vein and immediately combined with a 1/10 volume of 3.8% sodium citrate. It was centrifuged at 180 × *g* for 10 min to separate the supernatant as platelet-rich plasma (PRP). Platelet-poor plasma (PPP) was collected as the supernatant after centrifugation of the sediment at 2000 × *g* for 15 min. The platelet count in the PRP was adjusted to approximately $30 \times 10^4/\mu L$. Platelet aggregatability was determined spectrophotometrically according to the method of Born and Cross,[4] with an aggregometer PAM-8T (Mebanics Inc., Tokyo, Japan) and ADP (Sigma Chemicals, St. Louis, MO, USA) as an inducer of aggregation.

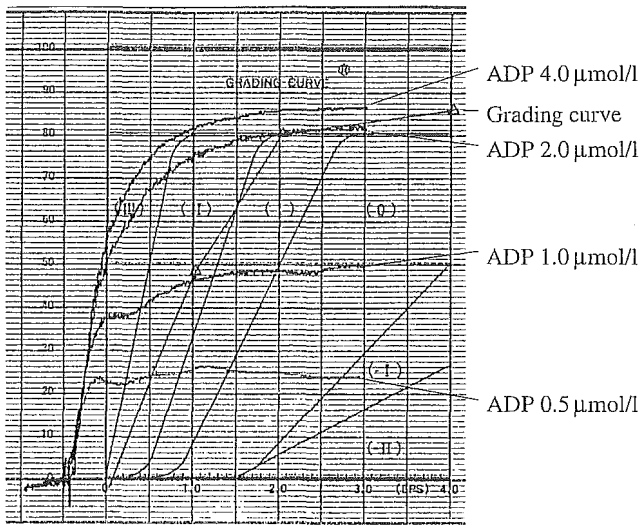

Figure 1 Representative findings of platelet aggregatability test. The grading curve is produced by plotting four concentrations (0.5, 1.0, 2.0 and 4.0 µmol/L) of adenosine-5′-diphosphate (ADP) along the horizontal axis, and plotting their individual rates (%) of aggregation 5 min after administration along the longitudinal axis. The degree of platelet aggregation is classified in six grades, raging from marked increase to marked decrease.

Using an aggregometer and ADP at four different concentrations (final concentrations of 0.5, 1.0, 2.0, and 4.0 µmol/L) as an agonist, the grading curve (GC) type was calculated on the basis of data at 5 min for each ADP concentration (Fig. 1). The GC type, consisting of six grades from +3 to –2, was evaluated in a programmed manner by connecting four plotted points of ADP concentration (µmol/L) at the point corresponding to the maximum aggregatory rate on the grading curve.

A GC type –2 or –1 indicated suppressed platelet aggregatability, while a GC type 0 or +1 indicated normal platelet aggregatability. (According to the GC type, increased platelet aggregatability is defined as the condition in which irreversible aggregation is induced by an ADP concentration of 1.0 µmol/L or less, while suppressed platelet aggregatability is defined as the condition in which biphasic aggregation in the range of 25–50% or reversible aggregation is induced by an ADP concentration of 4.0 µmol/L).[5] These procedures were completed within 3 h after blood sampling.

The reproducibility of platelet aggregatability results was examined by using two samples obtained at

intervals of 3–6 months from patients who received no antiplatelet therapy (n = 143).

Brain CT

A brain CT was performed on all of the patients. CT findings were classified into four types according to the location of low density areas: small deep infarction (in the penetrating branch region), brainstem infarction (in the brainstem or cerebellar region), cortical infarction (in the cerebral cortex and subcortex), and severe leukoaraiosis (Binswanger's type).

Risk factors and complications

Cases of hypertension were defined as those with a casual blood pressure of 140 mmHg or more and a diastolic pressure of 90 mmHg or more or cases receiving antihypertensive drugs. Diabetes mellitus was defined a fasting blood glucose concentration of 126 mg/dL or more or receiving diet therapy and medication. Hyperlipidemia was defined as a fasting blood total cholesterol concentration of 220 mg/dL or more or receiving diet therapy and medication. Cigarette smoking was defined as having a smoking index of 200 or more (number of cigarettes per day times years of smoking). Cases of ischemic heart disease were defined as those with a previous history of myocardial infarction or angina pectoris, or ischemic change of the ST segment on electrocardiography.

Assessment of ADL status

The degree of activity of daily living (ADL) was assessed according to the modified Rankin scale mainly by evaluating transfer and walking ability; the independent status (scale 0, 1, 2, 3), the partial dependence (scale 4), and total dependence (scale 5).[7]

Follow-up investigation

A follow-up survey after enrollment (at the examination date of platelet aggregation test) was performed by checking clinical records or interviewing patients by telephone. The average follow-up period was 3.9 years. In patients, who died within the follow-up period, we confirmed the cause and the date of death from death certificates, and investigated other vascular events related to outcome. In deaths due to vascular events, stroke death was defined as a patient dying within 3 months after a stroke even when it was accompanied by pneumonia. Deaths due to cardiovascular disease included myocardial infarction as well as congestive heart failure, presumably due to ischemia.

The results of platelet aggregatability tests were reported to all patients who had increased platelet aggregatability, and they were advised to undergo evaluation of vascular disease. Antiplatelet therapy was considered according to the diagnosis by electrocardiogram, ultrasonography of the carotid artery and brain CT. An explanation was given to patients with no indication for antiplatelet therapy, who showed only increased platelet aggregatability and obtained oral consent from these patients to be observed without antiplatelet therapy. Consequently, antiplatelet therapy was performed in 50 cases optionally during the follow-up period. There were 27 cases of atherothrombotic infarction, 12 cases of transient ischemic attack, four cases of cardiac infarction, and seven cases of peripheral artery occlusive disease. In contrast, antiplatelet therapy was not performed in 92 cases with small deep infarctions in the penetrating branch territory, two cases of brainstem infarction, and four cases of arteriosclerosis obliterans, in which symptoms were treated using other methods.

Statistical analysis

Statistical analysis was performed using StatView software (SAS Institute Inc., Cary, NC, USA). Analysis of variance (Fisher's protected least significant difference), Fisher's exact probability test, and the Kruskal–Wallis rank test were used to compare variables among groups. Coincidence coefficients (κ) for the reproducibility of platelet aggregatability tests were determined with the McNemar test. Life-table analysis was used to determine cumulative survival outcomes for each group. The log–rank test was used to compare life-table differences. The Cox proportional hazard model was used to analyze the variables influencing vascular event-related deaths. A P-value less than 0.05 was considered to indicate a statistically significant difference.

Results

(1) Background of each group

The mean age of each group ranged from 76.3 to 78.0 years (Table 1). Compared to Groups I and II, the mean age and male/female ratio were both high in Group III. There were no significant difference in ADL status, clinical stage of circulatory disturbance, frequency of each vascular risk or brain CT findings among the groups, except for diabetes, which was frequently seen in 26% of Group III (Table 2).

(2) Reproducibility of platelet aggregatability test results

Table 3 shows the distribution of platelet aggregatabilities from the first and second examinations. The coincidence rate for the reproducibility of the platelet aggregatability test was 0.72 (κ = 0.37), and McNemar statistics were indicated to be less than 5.991 (χ^2 = 0.05).

Table 1 Clinical findings for each group

	Group I	Group II	Group III	Total
n	40	208	99	347
Age (years: mean ± SD)	76.3 ± 9.3	76.5 ± 7.4	78.0 ± 7.0*	77.0 ± 7.6
Gender (M/F)	22/18	103/105	36/63*	161/186
Clinical diagnosis (%)				
Stroke	6 (15.0)	54 (26.0)	20 (20.2)	80 (23.1)
Cerebral thrombosis	4 (10.0)	48 (23.1)	19 (19.2)	71 (20.5)
Cerebral embolism	1 (2.5)	1 (0.5)	0 (0)	2 (0.6)
Cerebral bleeding	1 (2.5)	5 (2.4)	1 (1.0)	7 (2.0)
Transient ischemic attack	2 (5.0)	8 (3.9)	2 (2.0)	12 (3.5)
Vascular dementia	2 (5.0)	3 (1.4)	10 (10.1)	15 (4.3)
Ischemic heart disease	4 (10.0)	9 (4.3)	1 (1.0)	14 (4.0)
Arteriosclerosis obliterans	2 (5.0)	3 (1.4)	6 (6.1)	11 (3.2)
Dizziness	10 (25.0)	49 (23.6)	18 (18.2)	77 (22.2)
Senile dementia of Alzheimer's disease	3 (7.5)	7 (3.4)	4 (4.0)	14 (4.0)
Parkinson's disease	2 (5.0)	10 (4.8)	3 (3.0)	15 (4.3)

*$P < 0.05$ vs groups I and II (ANOVA, Fisher's PLSD, Fisher's exact probability test).

Table 2 Clinical characteristics of each group

	Group I	Group II	Group III	Total
n	40	208	99	347
Activities of daily living status (%)				
Independent	27 (67.5)	138 (66.4)	60 (60 6)	225 (64.8)
Partially dependent	10 (25.0)	54 (26.0)	27 (27.3)	91 (26.2)
Totally dependent	3 (7.5)	16 (7.7)	12 (12.1)	31 (8.9)
Clinical stage (%)				
1: Non-vascular	14 (35.0)	82 (39.4)	43 (43.4)	139 (40.1)
2: Circulatory disease	11 (27.5)	54 (26.0)	19 (19.2)	84 (24.2)
3: Thrombotic disease	15 (37.5)	72 (34.6)	37 (37.4)	124 (35.7)
Vascular risks (%)				
Hypertension	23 (57.5)	106 (51.0)	52 (52.5)	181 (52.2)
Diabetes	3 (7.5)	38 (18.3)	26 (26.3)*	67 (19.3)
Hyperlipidemia	12 (30.0)	72 (34.6)	33 (33.3)	117 (33.7)
CT findings (%)				
Low-density area (–)	25 (62.5)	129 (62.1)	62 (62.6)	216 (62.3)
Low-density area (+)	15 (37.5)	79 (37.9)	38 (37.4)	131 (37.7)
Small deep infarction	10 (25.0)	55 (26.4)	27 (27.3)	92 (26.5)
Brainstem infarction	0 (0)	2 (1.0)	0 (0)	2 (0.6)
Cortical infarction	3 (7.5)	19 (9.1)	5 (5.1)	27 (7.8)
Severe leukoaraiosis	2 (5.0)	3 (1.4)	5 (5.1)	10 (2.9)

*$P < 0.05$ vs group I (Fisher's exact probability test).

(3) Prognosis of each group

Mortality rate

Death occurred in three cases in Group I, 33 cases in Group II and 30 cases in Group III (Table 4). The annual mortality rates of Groups I, II, and III were 2.1%, 4.0%, and 7.5%, respectively, indicating a significantly high mortality rate in Group III. The Kaplan-Meier survival curves also showed survival rates of 0.92 (Group I), 0.84 (Group II) and 0.70 (Group III) with statistical significance among the groups (log–rank statistics = 9.173, Df = 2, $P = 0.0102$).

Causes of death

Among causes of death, pneumonia was seen in half (33 cases) of the 66 deaths. In Group III, 15 patients died of

cerebral infarction, of which five cases were of recurrent cerebral infarction (2 cases with athrothrombotic brain infarction, two cases with lacunar infarction, and one case with Binswanger's disease). The recurrent type of each case was the same as the initial type except for the case with Binswanger's disease, in which the patient had lacunar infarction during the follow-up period. In contrast, none of the patients in Groups I or II died of cerebral infarction. Death due to ischemic heart disease was seen in one case in Group I, five cases in Group II, and two cases in Group III. Subsequently, death due to vascular events was seen in one case in Group I, five cases in Group II, and 17 cases in Group III, indicating a significantly higher mortality rate in Group III (4.2%) than in Groups I and II (0.7% and 0.6%, respectively) (log-rank statistics = 21.607, Df = 2, $P < 0.0001$) (Fig. 2).

Table 3 Reproducibility: distributions of platelet aggregatory findings at 6-month intervals

	2nd Examination			Total
	Group I	Group II	Group III	
1st Examination				
Group I	8	5	0	13
Group II	8	66	11	85
Group III	0	17	28	45
Total	16	88	39	143

All figures indicate numbers of cases.

Mortality rates due to vascular events

Antiplatelet therapy was performed in approximately 15% of each group, of which one case in Group I ($n = 5$), nine cases in Group II ($n = 32$) and seven cases in Group III ($n = 13$) resulted in death. Consequently, annual mortality rates in patients treated without

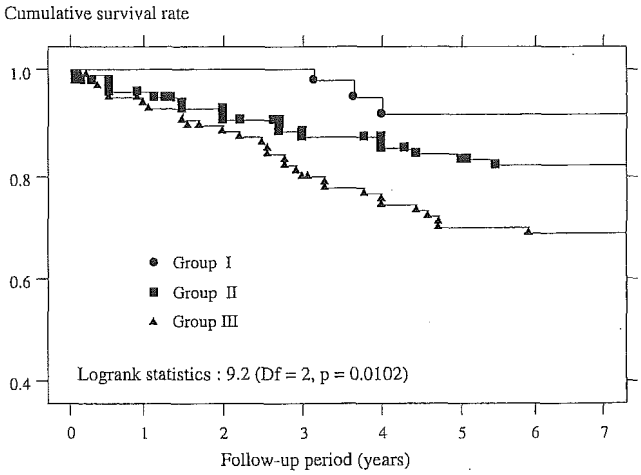

Figure 2 Kaplan-Meier survival curve of each group.

Table 4 Outcomes for each group

	Group I	Group II	Group III	Total
No. of subjects	40	208	99	347
Follow-up period, years: mean ± SD	3.6 ± 2.2	4.0 ± 1.9	4.1± 2.0	3.9 ± 2.0
No. of deaths	3	33	30	66
Cumulative mortality rate, percentages	7.5	15.9	30.3	19.0
Annual mortality rate, percentages	2.1	4.0	7.5*	4.8
Cause of death, numbers of cases				
Pneumonia	2	20	11	33
Cerebral infarction	0	0	15	15
Ischemic heart disease	1	5	2	8
Malignancy	0	6	2	8
Subarachinoid hemorrhage	0	1	0	1
Dehydration	0	1	0	1
Thrombotic diseases	1	5	17	23
Cumulative mortality rate, percentages	2.5	2.4	17.2	6.6
Annual mortality rate, percentages	0.7	0.6	4.2*	1.7
No. of subjects without antiplatelet treatment (%)	35 (87.5)	176 (84.6)	86 (86.7)	297 (85.6)
No. of deaths	2	24	23	49
Cumulative mortality rate, percentages	5.7	13.6	26.7	16.5
Annual mortality rate, percentages	1.6	3.5	6.6*	4.2
No. of deaths due to thrombotic disease	0	4	13	17
Cumulative mortality rate, percentages	0	2.8	13.9	6.7
Annual mortality rate, percentages	0	0.7	3.5	1.5

Table 5 Cox proportional hazards regression analysis of possible determinants of death (n = 347)

Variables	Hazard ratio	95% Confidence interval	P
GC type (vs GC type of −2 or −1)			0.0254
GC type of 0 or +1	1.307	0.979–1.745	0.0689
GC type of +2 or +3	1.757	1.157–2.669	0.0082
Activities of daily living status (vs independent)			0.0428
Partially dependent	1.342	0.931–1.933	0.1147
Totally dependent	1.619	1.111–2.360	0.0122
CT findings (vs low density area [–])			0.4556
Small deep infarction	0.859	0.298–2.473	0.7779
Brainstem infarction	1.161	0.407–3.310	0.7803
Cortical infarction	1.575	0.167–14.818	0.6914
Severe leukoaraiosis	1.167	0.374–3.642	0.7903
Hypertension (vs absent)	1.120	0.873–1.436	0.3718
Diabetes (vs absent)	1.115	0.809–1.536	0.5069
Hyperlipidemia (vs absent)	1.034	0.793–1.347	0.8060
Gender (vs women)	1.103	0.853–1.427	0.4545
Age (vs ≤ 69 years)			0.6292
70–79 years	0.844	0.583–1.221	0.3677
≥ 80 years	0.988	0.756–1.293	0.9321
Clinical stage (vs non-vascular [1])			0.6076
Circulatory disease [2]	0.722	0.380–1.374	0.3217
Thrombotic disease [3]	0.759	0.396–1.456	0.4072

GC, gradient curve.

antiplatelet drugs was 1.6% in Group I, 3.5% in Group II and 6.6% in Group III (log–rank statistics = 7.607, Df = 2, P = 0.0223). The annual mortality rates due to vascular events in patients treated without antiplatelet drugs was 0% in Group I, 0.7% in Group II and 3.5% in Group III, although log–rank statistics analysis could not be done since none of the patients in Group I died (among groups I + II and III, log–rank statistics showed 13.044 (Df = 1, P = 0.0003)).

Outcomes in patients receiving repeated platelet aggregatability tests

Death occurred in 12 cases of Group II and eight cases of Group III after the first examination. In Group II, platelet aggregation was accelerated in 11 cases, two of these patients died due to dehydration and ischemic heart disease, respectively. In contrast, none of 17 patients in Group III, who showed normal results on the second examination, died.

(4) Factors influencing mortality and their degree

Using age, gender, clinical stage of circulatory disturbance, ADL status, vascular risk (hypertension, diabetes, hyperlipidemia), brain CT findings and platelet aggregatability as independent variables, and total mortality as a dependent variable, the Cox proportional hazard model showed that total mortality was influenced by platelet aggregatability and ADL status (the hazard ratios were 1.8 and 1.6, respectively) (Table 5).

In the same manner, the Cox proportional hazard model showed that the mortality due to vascular events as a dependent variable was influenced by platelet aggregatability and clinical stages 2 and 3 (the hazard ratios were 1.5, 0.4 and 0.5, respectively) (Table 6).

Discussion

Platelet aggregatability depends on multiple factors in a milieu of flowing blood, in which endothelial cells play an important role in regulating the functions of circulating platelets.[8,9] Endothelial cell damage therefore could accelerate platelet aggregation and induce pathological thrombosis on the basis of platelet–endothelium imbalance.[8,9] Endothelial cell damage is usually associated with progressive arteriosclerosis, which becomes more frequent in the elderly. However, it still remains unclear how the acceleration of platelet aggregation influences individual prognoses. The reason for this is that no method for evaluating platelet aggregatability has been uniformly accepted, and selection bias in subjects with a variety of background factors is present, as described below in the study limitation. In this paper, outcomes in the elderly were studied from the viewpoint of routine platelet aggregatability examinations.

Table 6 Cox proportional hazards regression analysis of possible determinants of death due to vascular events ($n = 347$)

Variables	Hazard ratio	95 % Confidence interval	*P*
GC type (vs GC type of –2 or –1)			0.0822
GC type of 0 or +1	1.247	0.954–1.631	0.1065
GC type of +2 or +3	1.541	1.034–2.295	0.0335
Activities of daily living status (vs independent)			0.0011
Partially dependent	1.220	0.867–1.718	0.2532
Totally dependent	1.363	0.954–1.947	0.0889
CT findings (vs low density area [–])			0.4385
Small deep infarction	0.627	0.295–1.331	0.2243
Brainstem infarction	0.793	0.380–1.655	0.5364
Cortical infarction	1.304	0.267–6.376	0.7434
Severe leukoaraiosis	0.886	0.394–1.994	0.7707
Hypertension (vs absent)	1.156	0.916–1.459	0.2230
Diabetes (vs absent)	1.116	0.830–1.501	0.4675
Hyperlipidemia (vs absent)	1.029	0.803–1.318	0.8222
Gender (vs women)	1.043	0.821–1.326	0.7296
Age (vs ≤ 69 years)			0.3354
70–79 Years	0.782	0.552–1.107	0.1657
≥ 80 Years	0.984	0.767–1.263	0.9005
Clinical stage (vs non-vascular [1])			0.0011
Circulatory disease [2]	0.412	0.256–0.664	0.0003
Thrombotic disease [3]	0.513	0.318–0.828	0.0063

GC, gradient curve

In our study, the annual mortality rate and Kaplan-Meier survival curve demonstrated poor outcomes in Group III, in which major causes of death were cerebral infarction and pneumonia. The Cox proportional hazard model showed increased platelet aggregatability as an independent risk factor for death due to thrombosis. These findings indicate that patients with increased platelet aggregatability have poor outcomes due to lethal atherothrombotic disease. One of the reasons is considered to be the existence of advanced arteriosclerotic lesions in this group as ulcerated, ruptured, or stenotic athromatous plaques.[10,11] Such vascular lesions with endothelial damage could activate platelets due to decreased production of prostacyclin and nitric oxide within the endothelial cells, and through the exposure of platelets to the subendothelial tissue.[8,9,11]

In addition to underlying advanced arteriosclerosis, platelet activation would promote thrombus formation in lesions to induce obstruction of the artery, resulting in infarction of important organs such as the brain. Death due to ischemic heart disease was less frequent than death due to cerebral infarction. For this reason, it seems that the prevalence of these atherothrombotic diseases in Japan are different from those in Western countries.[12] Non-lethal vascular events including cerebral infarction, transient ischemic attack, ischemic heart disease and peripheral artery disease were not studied since our study was retrospective. It is difficult to completely assess non-lethal vascular events, which have shown mild to severe symptoms. However, the high mortality rate due to vascular events in Group III suggests that non-lethal vascular events occur more frequently in Group III and indicates that we are seeing only the tip of the iceberg as far as lethal vascular events are concerned.

Furthermore, activated platelets release growth factors, which stimulate the smooth muscle cells in the media to multiply and migrate into the intima, resulting in atheroma formation.[11,13,14] The vicious interaction between platelet activation and atheroma could accelerate atherothrombotic disease. Considering the constant decrease in survival rate during the observation period and the good reproducibility of platelet aggregatability test results, it seems that increased platelet aggregation always indicates a condition prone to the occurrence of atherothrombotic diseases. This indicates that platelet aggregatability is a predictor for further atherothrombotic vascular events, some of which are fatal.

In general, various factors influencing survival rate are considered in this study. First, underlying diseases such as clinically diagnosed vascular diseases, clinical stages of circulatory disturbance, and vascular risks themselves are possible major factors for prognosis. In particular, epidemiological studies have revealed that the occurrence of death due to vascular events is associated with a variety of risk factors such as hypertension,

hyperlipidemia, diabetes etc.[15–17] This association has also been verified by many intervention trials.[18,19] However, no significant difference could be found in the frequency of major risk factors except for diabetes. Diabetes is frequently associated with dysfunction of platelets.[20] In terms of relative frequency of clinical stages, there was also no significant difference among the groups at the baseline, but the hazard ratios for death due to vascular events were unexpectedly low in the advanced clinical stages. For this reason, antiplatelet therapy in the follow-up period could presumably affect the outcomes in these patients.

ADL status, cognitive functions and swallowing functions have been known to influence prognosis, especially in patients after a stroke.[21,22] In this study, one fourth of the subjects suffered from stroke. For this reason, it is considered that dependent ADL status, dementia or disturbance of swallowing could be accompanied by pneumonia, which was seen in 33 of 66 patients who died in our study.[21] The Cox proportional hazards regression analysis showed that totally dependent ADL status was an independent prognostic factor for overall death (hazard ratio; 1.619, $P = 0.0122$).

Study limitations

Some limitations were considered to be present in our study, especially in the evaluation of platelet aggregatability and selection bias in the subjects. Our study used the GC type obtained from *ex vivo* platelet aggregatability tests according to Born's turbidimetric method,[3,4] and applied ADP as an inducer chosen from several materials available for activating platelet. It is unclear to what extent the GC type using ADP corresponds to *in vivo* platelet aggregatability in the presence of various pathophysiological inducers. However, the GC type using ADP was valuable for monitoring patients treated with antiplatelet drugs,[5] and is widely used in clinical practice to obtain results with good reproducibility.

Reproducibility of the GC type showed a good coincident rate of 0.72 ($\kappa = 0.37$) between 143 paired samples at an interval of 3–6 months, although the selection bias should be taken into account in considering the results. In this study, the reproducibility of GC type was studied in patients with neither antiplatelet treatment nor acute thrombotic distress. Platelet aggregatability is usually suppressed not only by antiplatelet drugs,[1,6,23] but can be inconsistent in acute phases of thrombotic diseases, since platelets are accelerated to form thrombus or activated platelets have already been consumed.[3,24,25]

Conclusion

Although prognosis of the elderly was influenced by many intermingled factors, our study showed increased platelet aggregatability as an indicator for poor prognosis. It seems that the platelet aggregatability test was useful not only for monitoring patients with antiplatelet treatment, but also in detecting high-risk groups for poor prognosis due to vascular events. Furthermore, it suggests that antiplatelet treatment can be indicated for elderly patients with increased platelet aggregatability which clarifies the cause of the increased aggregatability.

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