2. Research design and method

2.1. Patient selection

Between April 1997 and March 2000, 342 patients were enrolled in this study. All patients were ambulatory and were either referred to our geriatric clinic (Nagoya University Hospital) or enrolled in our hospital to receive educational hospitalization for diabetes. Among them, 176 patients who were older than 65 years and who underwent an exercise-tolerance treadmill test were prospectively enrolled and followed for 4.1±0.5 years (Table 1). All patients gave their informed consent to participate in this study. None of the patients had experienced a myocardial infarction in the 3 months prior to enrollment, and they were independently active in daily life, as determined by their Lawton and Berthal scores (Collin, Wade, Davies, & Horne, 1988; Lawton & Brody, 1969).

2.2. Protocol and method

TMT was performed according to a protocol for the elderly, which we adapted from a protocol used for veterans in the United States (Prakash, Myers, & Froelicher, 2001). We changed the test so that each step lasted 2 min due to the age-related limitation of exercise tolerance (Hagberg, 1994; Tamesis et al., 1993; Table 2). The chronotropic response to exercise was assessed by estimating the proportion of the heart-rate reserve (220-age) used at peak exercise (Lauer, Francis, Okin, et al., 1999). Ischemic changes in the treadmill test were diagnosed using the Minnesota protocol; in brief, 1.0 mm or more ST segment elevation or depression in two or more leads was identified as positive. Exercise tolerance was estimated as METS, which was calculated from the participant's TMT results, body weight, age, and estimated Vo2 at rest. Plasma lipid and glucose levels were also measured. The diagnosis of hypercholesterolemia (HC) and diabetes followed the guidelines of the American Heart Association and Diabetes Association (Krauss, Eckel, Howard, et al., 2000; Resnick, Harris, Brock, et al., 2000). This study was approved by our institutional review board.

2.3. Follow-up data/definition of adverse outcome

All patients were followed until April 2002, with the mean follow-up period being 4.1±0.5 years after the treadmill test. The outcome was determined from patient interviews, hospital chart reviews, and telephone interviews. An adverse outcome was defined as the finding of significant stenosis in coronary angiography (CAG) with or without coronary intervention, such as percutaneous coronary angioplasty or ischemic cardiac events in the follow-up term. Cardiac events were defined as cardiac death, nonfatal MI, and resuscitated ventricular fibrillation or tachycardia after the TMT. Only the most severe outcome was considered an endpoint. Twenty-nine patients were excluded because of patient or physician refusal to follow-up (n=13), an inability to repeat the exercise treadmill test safely due to hearing loss (n=2), or geographic relocation (n=14). A total of 147 elderly individuals could be followed, and data on their histories of ischemic coronary disease, results of CAG, medication, and other parameters were recorded (Table 1). Based on the odds ratios evaluated as described below, patients older than 65 years were divided into four groups: Gp HC, hypercholesterolemic patients (n=42); Gp diabetes mellitus (DM), diabetic patients (n=30); Gp HC+DM, hypercholesterolemic and diabetic patients (n=36); and Gp C, nondiabetic and nonhyperlipidemic patients (n=39).

Table 1
Profile of patients

Patients number	147 (Male 71, Female 76)
Age (years)	71.7+0.4
Hypercholesterolemia	78 (Male 38, Female 40)
Diabetes mellitus (DM)	66 (Male 32, Female 34)
Hypertension	78 (Male 40, Female 38)
[Hypercholesterolemia+DM]	[36 (Male 17, Female 19)]

Table 2
Protocol of treadmill test for elderly

Stage	1	2	3	4	5	6	7	8	9
Period (min)	2	2	2	2	2	2	2	2	2
Speed (miles/h)	1	2	2	2	2	2	2.5	3.3	3.3
Gradient (%)	0	0	5	10	15	20	20	20	25
METs	2.5	3	5	6	8	9	10	11	13

2.4. Statistical analysis

Continuous data were expressed as the means±S.D. Categorical variables were analyzed by the chi-square test or Fisher's Exact Test. Continuous variables within groups were analyzed by repeated measures using analysis of variance (ANOVA). The Student's t test was used to identify significant differences in means. Stepwise multiple logistic regression analyses were used to identify the independent predictors of outcome, as well as the additive prognostic values of the clinical data and the exercise treadmill test. Fisher's Exact Test was used to calculate odds ratios or the probability of detecting any variables included in the logistic regression analysis in patients with adverse outcomes relative to patients with good outcomes.

3. Results

The odds ratios of each risk factor as determined by logistic regression analysis are shown in Table 2. Briefly, the odds ratios were as follows: DM, 4.167; HC, 4.485; and DM+HC, 8.652 (P<.01, respectively). That of age was significantly high (2.953; P<.05), whereas that of hypertension was not significant (2.151; P=.053). Notably, the odds ratio for positive ischemic signs as evaluated by TMT was 17.59.

Table 3
Odds ratio and 95% CI of each risk factor by logistic regression analysis

Hypercholesterolemia	4.485* (1.495–12.28)
DM	4.167* (1.477–10.81)
DM+Hypercholesterolemia	8.652* (2.543–13.68)
Hypertension	2.151 (0.845–9.26)
Age	2.953** (0.985–10.36)
Positive finding in TMTest	17.590*** (6.77–47.02)

* $P<.01$.
** $P<.05$.
*** $P<.001$.

We therefore divided the patients into four groups (Table 3): Gp HC, hypercholesterolemic patients (n=42; 72.0±0.5 years old; LDL-C, 150.7±10.4 mg/dl; exercise tolerance, 6.4±0.2 METs); Gp DM, diabetic patients (n=30; 72.3±0.9 years old; HbA1C, 7.6±0.5 g/dl; disease duration, 12.0±1.2 years; 6.0±0.5 METs); Gp HC+DM, hypercholesterolemic and diabetic patients (n=36; 71.4±0.8 years old; LDL-C, 149.5±11.5 mg/dl; HbA1C, 7.0±0.3 g/dl; disease duration for diabetes, 12.9±1.1 years; 6.4±0.3 METs); and Gp C, nondiabetic and nonhypercholesterolemic patients (n=39; 71.6±0.9 years old; 6.2±0.4 METs). The mean age and the frequency of other coronary risk factor complications, such as hypertension, smoking, and others, were not significantly different among the four groups. The TMT-positive ratios were 28.6%, 33.3%, 52.7%, and 16.3% in participants from the Gp HC, DM, HC+DM, and C groups, respectively (Fig. 1). Only three participants complained of chest pain during the TMT test (two in Gp HC+DM and one in Gp HC), and all of them became symptom-free within 5 min after exercise; all other positive patients were symptom-free. The ratios of patients receiving CAG per TMT-positive patient within 8 months after TMT were 66.7%, 63.6%, 68.4%, and 62.5% in the Gp HC, DM, HC+DM and C groups, respectively. CAG was not done for the following reasons: (1) patient refusal, lack of understanding of the CAG, and/or coronary intervention due to risk (n=11); (2) a high risk of coronary intervention for other general diseases such as chronic renal failure or cerebral infarction (n=6); and (3) physician refusal due to the risk of coronary intervention or CAG because of cognitive impairment, and others (n=6). In some patients who did not receive CAG but were suspected to have stenotic lesion by other examinations, medication such as anti-platelets and/or NO donors, such as isosorbide dinitrate, was prescribed. More than 75% stenosis was observed in 75.0%, 71.4%, 69.2%, and 60.0% of CAG-receiving patients of the Gp HC, DM, HC+DM, and C groups, respectively, and coronary intervention was performed in all of these cases (Fig. 1). During the 4.1±0.5 years of observation, ischemic coronary diseases such as angina pectoris or acute myocardial infarction occurred in 4.7% (8.3), 3.3% (10.0), 5.5% (5.3), and 0% of patients in the Gp HC, DM, HC+DM, and C groups, respectively (the percentage for TMT-positive patients). Older patients (older than 75 years of age) had more events (7.3% vs. 0%) than did the relatively younger patients (65–74 years; $P<.001$). Cardiac death was significantly more frequent in older

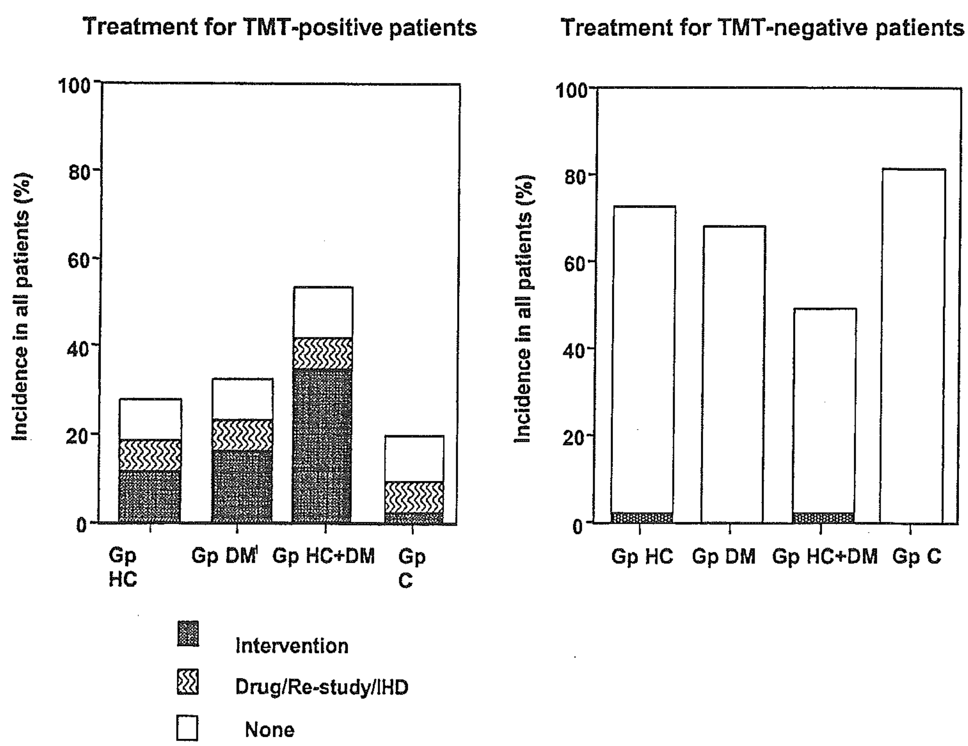

Fig. 1. Left: The frequency of TMT-positive findings and the corresponding treatments chosen for each disease group. Gp HC: hyper-cholesterolemic patients (n=42); Gp DM: diabetic patients (n=30); Gp HC+DM: hypercholesterolemic and diabetic patients (n=36); Gp C: nondiabetic and nonhypercholesterolemic patients (n=39). Right: The frequency of TMT-negative findings and the corresponding treatments chosen for each disease group.

Table 4
Patients profile who have coronary stenosis by CAG study, acute coronary syndrome, or drug treatment without CAG

	Percentage (%) of possible IHD				
	Total	In TMT-positive patients	In TMT-negative patients	Sensitivity of TMT for IHD	Specificity of TMT for IHD
Gp HC (42)	23.2	75.0	5.6	72.7≦	96.7
Gp DM (30)	26.7	72.7	0	66.7≦	100
Gp HC+DM (36)	41.7	73.7	5.9	68.8≦	94.1
Gp C (39)	10.3	66.7	0	66.7≦	100

Possible IHD means significant stenosis, ACS, and drug treatment during the observation term (4.1±0.5 years).
Sensitivity is calculated by (ACS and significant stenosis)/(TMT-positive patients−patients treated by drug without CAG).
Specificity is calculated by (no ACS or no significant stenosis)/(TMT-negative patients).

patients (P<.001). Finally, significant stenosis observed by CAG, IHD, or medical intervention during follow-up term was observed in 75.0%, 72.7%, 73.7%, and 66.7% of TMT-positive patients in the Gp HC, DM, HC+DM, and C groups, respectively. Sensitivity and specificity were calculated as shown in Table 4, and they mean the reliability and usefulness of TMT for the diagnosis or speculation of IHD.

4. Discussion

The elderly population is increasing all over the world, and Japan is now the world's most aged society. Elderly individuals with IHD have higher rates of physical disability, as defined by a diminished ability to perform the activities of daily living, than do persons without IHD. Older age and clinical manifestations of angina pectoris or chronic heart failure are known to be associated with the highest rates of disability (Morey, Pieper, Crowley, Sullivan, & Puglisi, 2002). The odds ratio for age was also found to be significantly high in the present study (2.953; P<.05).

TMT using a protocol for the elderly was shown in the present study to be safe and possibly useful for maintaining independent activities of daily living in the elderly, as the positive ischemic signs evaluated by TMT showed an odds ratio of 17.59 despite the fact that 90% of patients testing positive were asymptomatic. The exercise tolerance (mean=6.1±0.5 METs) determined in the present study indicates that the elderly have the capacity to maintain the activities of daily living, including voidance and using the stairs. The optimal test duration is from 8 to 12 min, and the protocol workloads should be adjusted to permit this duration (Myers & Froelicher, 1993).

The odds ratios for each risk factor, as determined by logistic regression analysis, were the following: DM, 4.167; HC, 4.485; and DM+HC, 8.652 (P<.01, respectively). Hypertension, however, was not found to be significant (2.151; P=.053). Although the importance of diabetes as a coronary risk factor is well known, almost all patients with a positive TMT test were asymptomatic and showed a relatively high percentage of coronary stenosis. TMT is useful in screening for diabetic coronary macroangiopathy. The frequency of the TMT-positive ratio was found to be relatively high in the present study; we speculate that this finding was due to the fact that the study participants had suffered from diabetes for long periods and to our adoption of the standards of the AHA exercise-tolerance test (Gibbons, Balady, Basley, et al., 1997). We also examined 166 patients younger than 65 years as young control participants; these patients underwent TMT using a symptom-limited modified Bruce protocol and were followed for 4.0±0.8 years (data not shown). Their positive ratios were less than 15%, even in the patients with diabetes complicated with hyperlipidemia (data not shown). Despite a paucity of data on the predictive value of stress tests in older populations, current stress-testing guidelines extend the following recommendations to all adults aged 65 and older (Gibbons et al., 1997). The value of exercise training in patients older than 65 years is supported by a recent study involving 772 men with coronary heart disease, in which physical activity (walking, in particular) for a total of at least 4 hours per week was associated with a significant reduction in overall mortality. Thus, TMT should be useful in cardiac-rehabilitation programs for the elderly. Regarding the interpretation of these findings, a number of limitations should be mentioned. Goyara, Jacobsen, Pellikka, et al. (2000) found that exercise capacity, but not ST-segment changes, was predictive of mortality and cardiovascular events, but they did not distinguish patients who were older than 75 years of age from those who were younger. These findings do not agree with those of the present study, although we cannot identify the reason for this discrepancy. In our study, some patients did not undergo CAG due to patient or physician refusal, and others. Although the risk associated with CAG is small, some physicians cannot justify it fully to patients. This study was also confined to those patients who were referred for exercise testing and thus were able to walk on a treadmill. Despite these facts, our results demonstrated conclusively that TMT was useful for the prevention and management of ischemic coronary artery disease in elderly patients, especially in those with diabetes.

Especially, the high value of specificity of TMT means that TMT-negative finding means the less possibility of IHD and that TMT can be used as screening test of IHD for independent elderly.

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