that the myocardial TG content measured using $^1$H-MRS is associated with age (6) and the presence of diabetes mellitus (7) and myocardial systolic dysfunction (4, 8, 9) or diastolic dysfunction (6, 10). In addition, progressive caloric restriction has been shown to induce a dose-dependent increase in the myocardial TG content (11), whereas endurance training reduces this parameter (12). We recently reported that the myocardial TG content is significantly lower in endurance athletes than in healthy subjects (13).

The aim of this study was to assess the associations between the myocardial TG content measured on $^1$H-MRS and metabolic parameters, cardiac morphology, the left ventricular function and exercise capacity in apparently healthy Japanese subjects.

## Materials and Methods

### Subjects

A total of 37 apparently healthy Japanese men were recruited through a local advertisement. All subjects were 20-61 years of age and not currently receiving any medical treatment. Individuals with findings of acute or chronic diseases on a medical examination were excluded. The ethics committee of Juntendo University approved the study protocol and all subjects provided their written informed consent before participating in this study, according to the guidelines of the Declaration of Helsinki.

### Measurements

Body composition was assessed in terms of skeletal muscle mass and body fat after overnight fasting using a multi-frequency bioelectrical impedance analysis with eight tactile electrodes (MF-BIA8; In-Body 720, Biospace, Seoul, Korea) (14). The subject's apparatus provides measurements of the fat mass, fat-free mass and percentage body fat. Each patient's personal activity level was assessed using the international physical activity questionnaire (IPAQ) (15).

Standard laboratory tests were performed under fasting conditions before the $^1$H-MRS procedure. Serum lipid profiles were determined according to enzymatic methods, including the total cholesterol (Symex, Kobe, Japan), high-density lipoprotein (HDL) cholesterol and triglyceride (Sekisui Medical, Tokyo, Japan) levels, using a BioMajesty JCA-BM8060 analyzer (Japan Electron Optics Laboratory, Tokyo, Japan). The Friedewald formula was used to calculate the level of serum low-density lipoprotein (LDL) cholesterol. The serum insulin level was assessed using a chemiluminescent enzyme immunoassay with the Lumipulse presto II analyzer (Fujirebio, Tokyo, Japan). The homeostasis model assessment index (HOMA-IR) was calculated to estimate the degree of insulin resistance based on the fasting insulin and glucose levels, as follows: insulin (μU/mL) × glucose (mmol/L)/22.5 (16). The free fatty acid (FFA) level was measured using a standard assay (Eiken chemical, Tokyo, Japan) and BioMajesty JCA-BM2250 analyzer (Japan Electron Optics Laboratory, Tokyo, Japan). The serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level was determined using an electrostatically controlled linear inchworm actuator on modular analytics (HITACHI Hi-Technologies, Tokyo, Japan). Finally, the HbA1c level was determined in whole-blood samples according to a latex-enhanced immunoassay (Fujirebio, Tokyo, Japan).

### MRI and MRS

Cardiac magnetic resonance imaging (MRI) and $^1$H-MRS were conducted on a MAGNETOM Avanto 1.5-Tesla MRI system (Siemens Medical Solution, Erlangen, Germany), as previously reported (13). In brief, each subject rested in the supine position with a belt placed around the upper part of the abdomen in order to minimize respiratory movements. LV functional and morphological parameters were determined using a specially designed software program (Argus; Siemens Medical Systems, Erlangen, Germany) (17, 18) on a separate workstation. The endocardial and epicardial LV borders were traced manually on short-axis cine images obtained at end-systole and end-diastole. The LV end-diastolic volume (EDV), LV end-systolic volume (ESV), LV ejection fraction and stroke volume were calculated using Simpson's method. Furthermore, the peak LV ejection and filling rates were automatically derived from LV volume-time curves.

In order to quantify the myocardial TG content, a 10×10×20-mm$^3$ voxel was positioned within the ventricular septum on cine dynamic cine-mode images (Fig. 1). The spectrum of water and lipids was acquired using point-resolved spectroscopy (PRESS) with a repetition time (TR) of at least 4,000 ms and echo time (TE) of 30 ms. The myocardial TG signals were acquired at 1.4 ppm from water suppressed spectra. The water signals were acquired at 4.7 ppm from non-water suppressed spectra (Fig. 1). The areas under the curves for the water and lipid peaks were quantified according to standard line-fitting procedures (Siemens Syngo Spectroscopy, Siemens Medical Solution). The myocardial TG levels are expressed as the lipid to water ratios (%) (13, 19-21).

### Measurement of cardiopulmonary fitness

An incremental cycling test was performed on a Corival 400 (Lobe B.V., Groningen, Netherlands) with an expiratory gas analyzer (Vmax-295, SensorMedics, Yorba Linda, USA) in order to measure the anabolic threshold (AT) and maximal oxygen consumption ($VO_{2max}$), as previously described (22). After three minutes of rest, a three-minute warm-up test was performed at 40 W, followed by ramp loading (15-30W/min) until subjective exhaustion. According to the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) guidelines, AT corresponds to the change in slope midrange of the $VO_2/VCO_2$ response curve (V-slope method). In cases in which the AT point was not identified on the V-slope, we used the point at which $VE/VO_2$ starts to increase while $VE/VCO_2$ remains constant, with VE corresponding to the total minute ventilation (23).

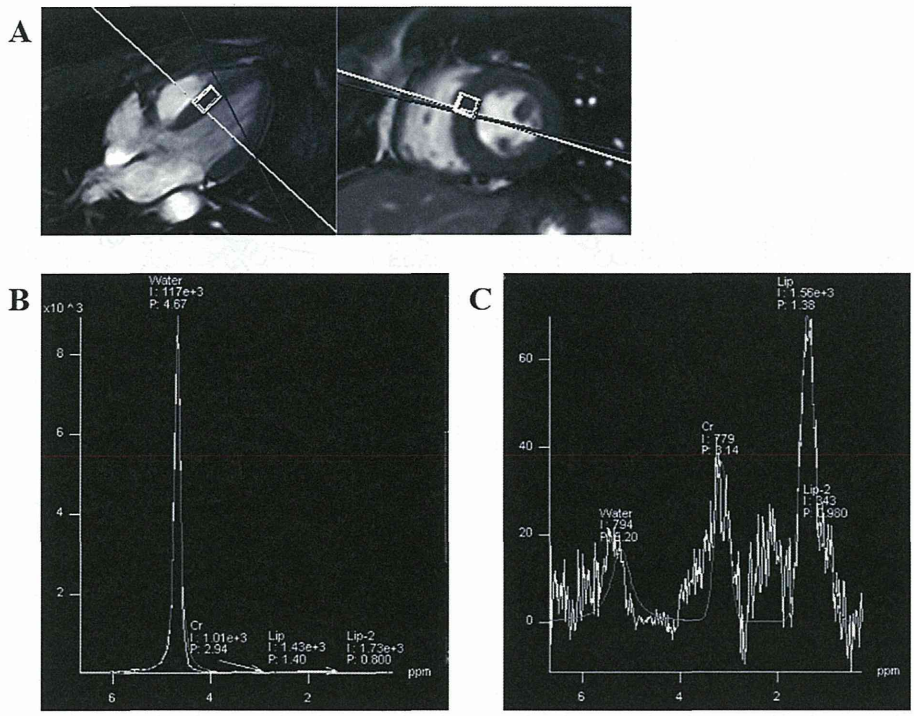


**Figure 1.** **Representative results of the $^{1}$H-MRS spectra in a healthy subject. A: Myocardial voxel localization for $^{1}$H-MRS in four-chamber and short-axis views. B: $^{1}$H-MR spectra without water suppression. C: $^{1}$H-MR spectra without water suppression.**

**Table 1.** **Clinical Characteristics**

| | Total (n = 37) |
|---|---|
| Age, years | 30.6 ± 8.1 |
| Body height, m | 1.728 ± 0.051 |
| Body weight, kg | 68.0 ± 6.5 |
| Body mass index, kg/m$^2$ | 22.7 ± 2.0 |
| Skeletal muscle mass, kg | 32.9 ± 8.3 |
| Body fat weight, kg | 13.0 ± 4.4 |
| Percent of body fat, % | 18.5 ± 5.4 |
| Neck circumference, cm | 37.0 ± 2.3 |
| Waist circumference, cm | 80.0 ± 5.7 |
| Total cholesterol, mg/dL | 183 ± 29 |
| Triglyceride, mg/dL | 102 ± 73 |
| LDL–cholesterol, mg/dL | 108 ± 29 |
| HDL–cholesterol, mg/dL | 55 ± 11 |
| Fasting free fatty acid, μEq/L | 326 ± 161 |
| Fasting blood glucose, mg/dL | 92 ± 8 |
| Insulin, μU/mL | 5.9 ± 3.7 |
| HOMA–IR | 1.3 ± 0.9 |
| HbA1c, % (NGSP) | 4.7 ± 0.2 |
| Creatinine, mg/dL | 0.83 ± 0.09 |
| eGFR, mL/min/m$^2$ | 91.6 ± 12.4 |
| NT-proBNP, ng/L | 15.1 ± 13.3 |
| Urinary acid, mg/L | 6.0 ± 0.9 |
| Anaerobic threshold, mL/kg/min | 19.0 ± 5.2 |
| $VO_2$max, mL/kg/min | 43.2 ± 8.0 |
| CAVI | 6.5 ± 0.7 |
| IPAQ score | 2,318 ± 1,605 |

Values are mean ± SD. LDL: low–density lipoprotein, HDL: high–density lipoprotein, eGFR: estimated glomerular filtration rate, HOMA–IR: homeostasis model assessment of insulin resistance, NT-proBNP: N–terminal pro brain natriuretic peptides, $VO_2$max: maximal oxygen intake, CAVI: cardio ankle vascular index, IPAQ: international physical activity questionnaire

**Table 2.** **MRI Variables**

| | Total (n = 37) |
|---|---|
| LV ejection fraction, % | 50.2 ± 5.4 |
| LV end diastolic volume, mL | 157 ± 26 |
| LV end systolic volume, mL | 77 ± 16 |
| Stroke volume, mL | 80 ± 14 |
| Cardiac output, L/min/m$^2$ | 4.9 ± 1.0 |
| LV myocardial mass, g | 124 ± 17 |
| Peak ejection rate, mL/sec | 608 ± 234 |
| Peak filling rate, mL/sec | 672 ± 251 |

Values are mean ± SD. LV: left ventricular

### *Evaluation of atherosclerotic parameters*

The parameter of atherosclerosis, the cardio-ankle vascular index (CAVI), was calculated automatically using the VaSera VS-1500 AN (Fukuda Denshi, Tokyo, Japan) (24, 25).

### *Statistical analysis*

The values are expressed as the mean ± standard deviation (SD). Variables not exhibiting a normal distribution were transformed into natural logarithmic values prior to the statistical analyses. Pearson's correlation coefficients were calculated between the myocardial TG content and the other parameters. In order to assess determinants of the myocardial TG content, we performed univariate and multivariable linear regression analyses. All statistical analyses were conducted using the SPSS version 20 software package (SPSS, Chicago, USA). A p value of less than 0.05 was considered to be statistically significant.

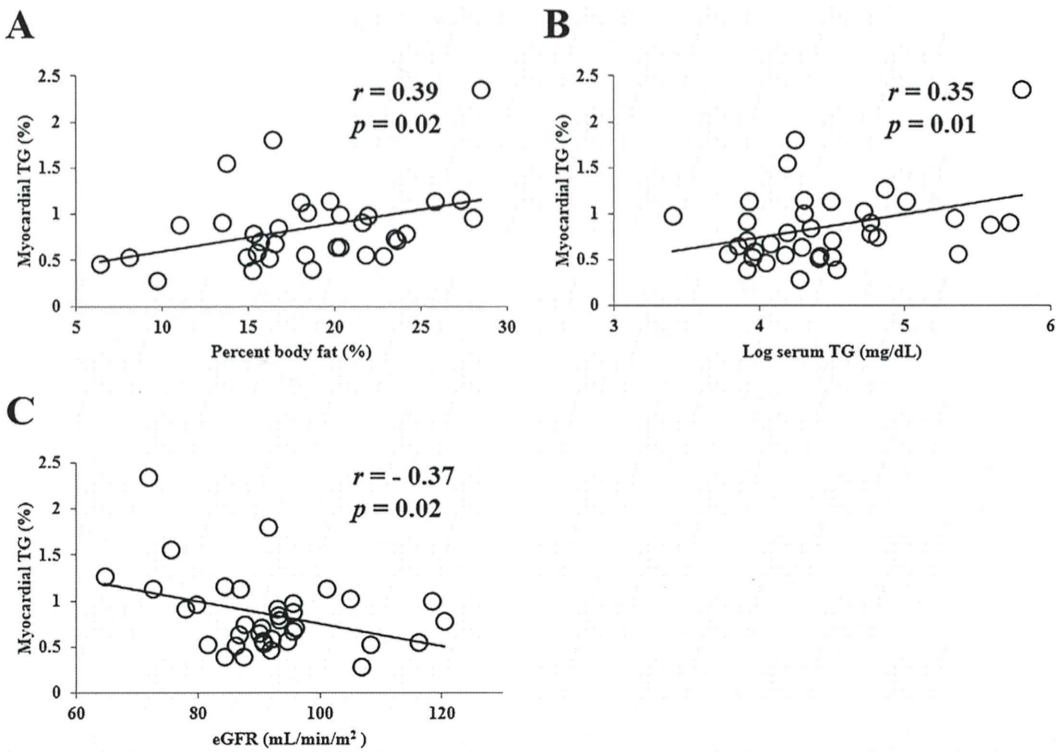


**Figure 2.** **Correlations between the myocardial TG content and the clinical variables. A: Correlation between the myocardial TG content and percent body fat. B: Correlation between the myocardial TG content and the serum TG level with logarithmic transformation. C: Correlation between the myocardial TG content and estimated glomerular filtration rate.**

## Results

The clinical characteristics of the study subjects are summarized in Table 1. The mean age was 30.5±8.1 years, the mean body mass index was 22.7±2.0 kg/m$^2$ and the mean maximum $VO_2$ was 43.2±8.0 mL/kg/min. None of the subjects were obese or had abnormal parameters on the blood analyses.

The MRI and MRS variables are shown in Table 2. None of the subjects had an abnormal ejection fraction, cardiac mass volume, peak ejection fraction or filling rate. The myocardial TG content was positively correlated with the percent body fat (r=0.39, p=0.02) and serum TG level (r= 0.35, p=0.001) (Fig. 2) and negatively correlated with the estimated glomerular filtration rate (eGFR; r=-0.37, p=0.02), AT (r=-0.36, p=0.02), maximal load of cardiopulmonary exercise testing (CPX) (r=-0.40, p=0.01), left ventricular end-diastolic volume (LVEDV; r=-0.42, p=0.01) and left ventricular end-systolic volume (LVESV; r=-0.51, p=0.01) (Fig. 3). No significant correlations were noted between the myocardial TG content and the CAVI (r=0.16, p=0.37) or and the IPAQ score (r=-0.25, p=0.14).

The AT level strongly correlated with the maximal CPX load (r=0.81, p<0.0001). The LVESV level also correlated with the LVEDV (r=0.82, p<0.0001). Moreover, the myocardial TG content and serum TG level were associated with insulin resistance and obesity, and the relationship between the myocardial TG content and the eGFR was affected by aging. Therefore, we performed a multivariate analysis including age, BMI, serum TG, eGFR and LVESV. In this model, the LVESV was an independent factor of the myocardial TG content (Table 3).

## Discussion

The present study demonstrated significant associations between the myocardial TG content and the percent body fat, serum TG level, eGFR, anaerobic threshold, maximal load of CPX, LVEDV and LVESV in apparently healthy Japanese subjects. In addition, the LVESV value was found to be an independent factor of the myocardial TG content.

The generation of myocardial TG is closely dependent on myocardial lipid metabolism. The accumulation of myocardial TG is primarily determined by the supply of the fatty acids and mitochondrial energy-producing efficiency (26). Moreover, myocardial lipid metabolism is regulated by a complex equilibrium between the supply of fatty acids to the heart, competing energy substrates, energy demand and supply of oxygen to the heart, uptake and esterification of fatty acids and control of the mitochondrial function (i.e. fatty acid oxidation and electron transport chain activity) (26). Therefore, it is important to assess the myocardial TG content using $^1$H-MRS noninvasively in the clinical setting.

Previous studies have reported that the myocardial TG

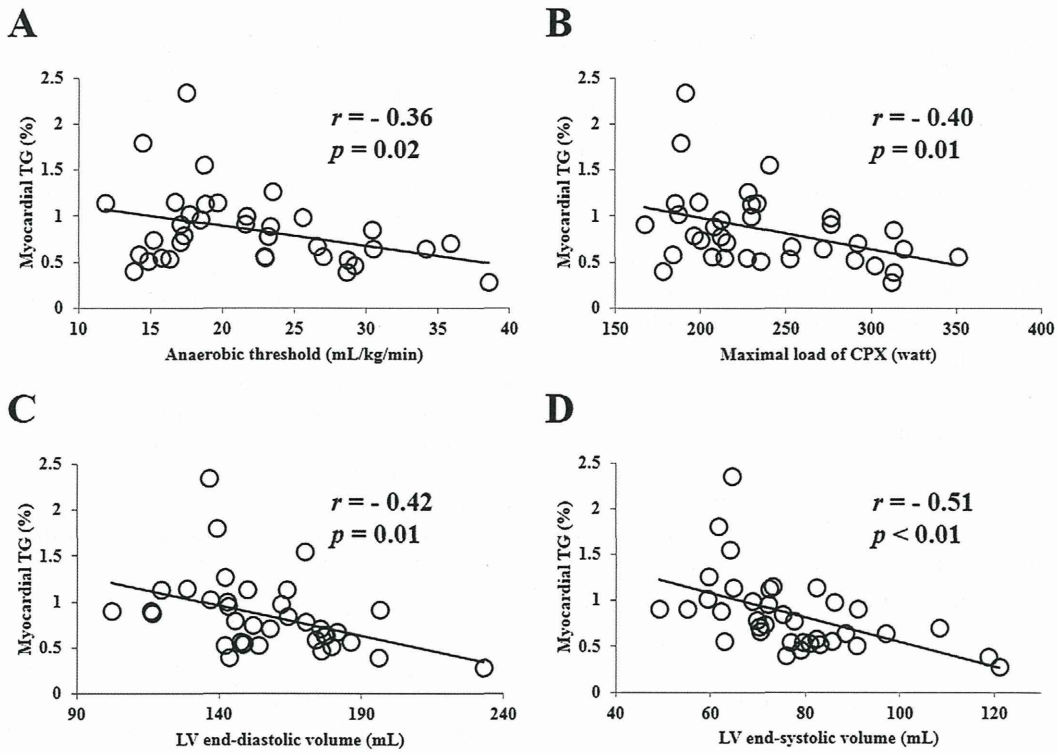


**Figure 3.** **Correlations between the myocardial TG content and the MRI parameters. A: Correlation between the myocardial TG content and anaerobic threshold. B: Correlation between the myocardial TG content and maximal load of cardiopulmonary exercise. C: Correlation between the myocardial TG content and left ventricular (LV) end-diastolic volume. D: Correlation between the myocardial TG content and LV end-systolic volume.**

**Table 3.** **Multivariable Linear Regression Analyses**

| Factors | ß | p value |
|---|---|---|
| Age | -0.0036 | 0.69 |
| BMI | 0.036 | 0.28 |
| Serum TG | 0.00099 | 0.22 |
| eGFR | -0.0070 | 0.22 |
| LVESV | -0.011 | 0.021 |

BMI: body mass index, TG: triglyceride, eGFR: estimated glomerular filtration rate, LVESV: left ventricular end-systolic volume

content is related to obesity, metabolic disorders and cardiac dysfunction (1, 2, 4, 5, 7, 27). The present study confirmed an association between the myocardial TG content and parameters of metabolic disorders, including the percent body fat and serum TG levels, even in apparently healthy subjects. These associations are supported by the well-established notion that increased body fat results in insulin resistance and high TG levels. In addition, a previous study suggested that the myocardial TG content is associated with obesity via a positive association with the plasma FFA concentration (8). However, we found no correlations between the FFA level and myocardial TG content in our healthy subjects (data not shown). The present study subjects did not include obese patients or those with impaired glucose tolerance with a decreased mitochondrial function. In addition, we enrolled several healthy subjects with exercise habits. Endurance exercise regulates lipoprotein lipase synthesis and the mitochondrial function, primarily β-oxidation (28). The background factors of the study subjects may therefore account for differences in results between the present study and previous reports.

In the current analysis, we found that morphological cardiac parameters were negatively correlated with the myocardial TG content, including the LVEDV and LVESV. In previous reports, the myocardial TG content has been shown to positively correlate with LV mass weight per LV volume according to the degree of LV hypertrophy (4). Furthermore, we recently reported that athletes exhibit lower myocardial TG levels (13). We also included several endurance athletes in the present study; however, similar trends were obtained after excluding these subjects (data not shown). Moreover, the LVESV level was found to be an independent predictor of the myocardial TG content. These data suggest that measuring the myocardial TG content is useful for assessing the relationship between cardiac remodeling and cardiac lipid metabolism, although further investigations are needed to clarify the precise mechanisms.

Finally, our data showed a negative correlation between the myocardial TG content and AT. A previous study demonstrated a negative relationship between the myocardial TG content and cardiopulmonary fitness in obese women (27). Reduced cardiorespiratory fitness predisposes to individuals to cardiovascular disease and predicts premature death (29, 30), and the level of cardiorespiratory fitness de-

pends on both the degree of obesity and age. Our next study will investigate the impact of clinical interventions on the myocardial TG content and exercise tolerance.

The present study is associated with several limitations. First, this was a single-center study with a small sample size. Second, we included only male subjects. Finally, we did not perform oral glucose tolerance tests. Therefore, some subjects with impaired glucose tolerance may have been included in our study population; however, no obese individuals or patients with impaired glucose tolerance with an obviously decreased mitochondrial function were assessed.

## Conclusion

$^{1}$H-MRS may be useful for noninvasively assessing the associations between the myocardial TG content and various clinical parameters, including those indicative of obesity, metabolic disorders, cardiac morphology and exercise capacity, even in healthy Japanese subjects.

**The authors state that they have no Conflict of Interest (COI).**

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Original article

# Long-term prognosis and clinical characteristics of young adults (≤40 years old) who underwent percutaneous coronary intervention

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ABSTRACT

*Background:* Limited data exist regarding the long-term prognosis of percutaneous coronary intervention (PCI) in young adults. The aim of this study was to retrospectively assess the long-term clinical outcomes in young patients who underwent PCI.

*Methods and results:* Between 1985 and 2011, 7649 consecutive patients underwent PCI, and data from 69 young adults (age ≤40 years) and 4255 old adults (age ≥65 years) were analyzed. A Cox proportional hazards regression analysis was used to determine the independent predictors of a composite endpoint that included all-cause death and acute coronary syndrome (ACS) during the follow-up period. The mean age of the 69 young patients was 36.1 ± 4.9 years, and 96% of them were men. Approximately 30% were current smokers, and their body mass index (BMI) was 26.7 ± 5.0 kg/m$^2$. The prevalence of diabetes and hypertension was 33% and 48%, respectively. All patients had ≥1 conventional cardiovascular risk factor. At a median follow-up of 9.8 years, the overall death rate was 5.8%, and new-onset ACS occurred in 8.7%. Current smoking was an independent predictor of the composite endpoint (hazard ratio 4.46, confidence interval 1.08–19.1, $p = 0.04$) for young adults.

*Conclusion:* Current smoking and obesity (high BMI) are the important clinical characteristics in young Japanese coronary heart disease patients who undergo PCI. The long-term prognosis in young patients is acceptable, but current smoking is a significant independent predictor of death and the recurrence of ACS in young Japanese coronary heart disease patients who are obese.



## Introduction

Coronary heart disease (CHD) is recognized as one of the lifestyle-related diseases [1]. Since lifestyle-related burden increases the risk of CHD events by age, CHD mainly occurs in patients over 40 years of age. On the other hand, young adults ≤40 years of age rarely suffer from CHD, and epidemiologic data show that this group accounts for only about 3% of all coronary artery disease (CAD) cases [2]. However, autopsies have shown that about 50% of young individuals have progressive coronary atherosclerosis even though they were not diagnosed with CHD [3].

Several studies suggest that young CHD patients already have multiple lifestyle-related risk factors and consequently have the potential to develop coronary atherosclerosis [4,5]. One study has shown that cigarette smoking, diabetes, and dyslipidemia are prominent risk factors for the development of early atherosclerosis in young populations [6]. Previous studies regarding differences in characteristics of CHD between younger and older patients demonstrated that smoking, obesity, and the presence of diabetes were associated with CHD in younger patients [7,8]. Despite multiple lifestyle-related risk factors, younger CHD patients have a better short-term clinical outcome compared with older CHD patients [9]. However, there are few reports investigating the long-term clinical outcome and the predictors of a poor long-term prognosis in young CHD patients.

Thus, the purpose of this study was to examine the long-term clinical outcomes and assess the predictors of a poor long-term prognosis in young patients (≤40 years old) who underwent percutaneous coronary intervention (PCI).

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## Methods

### *Patients and data collection*

Data from consecutive patients who underwent PCI at Juntendo University Hospital (Tokyo, Japan) between February 1985 and February 2011 were analyzed. The data collected on each patient included age, gender, body mass index (BMI), blood pressure (BP), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides, fasting blood glucose (FBG), smoking status, family history of CHD, medication use, revascularization procedure-related factors, and comorbidities. Young adults were defined as those ≤40 years of age, because that is the most commonly used cut-off point for young age in previous studies [10,11]. Hypertension was defined as a systolic BP ≥ 140 mmHg, a diastolic BP ≥ 90 mmHg or treatment with antihypertensive medications. Diabetes mellitus (DM) was defined as a fasting plasma glycemic level ≥126 mg/dl or treatment with oral hypoglycemic drugs or insulin injections. A current smoker was defined as one who smoked at the time of PCI or had quit smoking within 1 year before PCI. In all patients, indications for PCI were based on objective evidence of myocardial ischemia (positive stress test), ischemic symptoms or signs associated with significant angiographic stenosis. The hospital's internal review board approved this study. At our institution, informed consent to record patient data is obtained from all patients who undergo PCI.

The follow-up period ended on October 31, 2011. Survival data and data on incident acute coronary syndrome (ACS) were collected by serial contact with the patients or their families, and were assessed from the medical records of patients who had died or of those who were followed up at our hospital. Information about the circumstances and date of death were obtained from the families of patients who died at home, and details of the events or the cause of death was supplied by other hospitals or clinics where the patients had been admitted. All data were collected by blinded investigators. ACS was identified if patients had ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UAP). STEMI was determined based on symptoms of ischemia with ST-segment elevation on the electrocardiogram and increased serum levels of cardiac enzymes [troponin, creatine kinase (CK-MB, CK ≧2-fold increase] [12,13]. NSTEMI was determined based on symptoms of ischemia without ST-segment elevation on the electrocardiogram and increased serum levels of cardiac enzymes [14]. UAP was determined based on the symptoms of ischemia at rest or with a crescendo pattern of symptoms or new-onset symptoms associated with transient ischemic ST-segment shifts and normal serum levels of cardiac enzymes [14].

### *Statistical analysis*

The results are expressed as the mean ± SD for continuous variables and as a percentage for categorical variables. To determine factors associated with the composite endpoint of all-cause death and ACS, univariate Cox regression analysis was performed. Variables which had a significant or borderline significant association ($p < 0.10$) with the composite endpoint were included in multivariate Cox regression analysis along with age and gender as independent variables for both young and old adult groups. In young adults, BMI was added as a covariate because it was an important feature of young patients. Survival curves were drawn using the Kaplan–Meier method and the log-rank test was used to compare two survival curves. A $p$-value <0.05 was considered significant, unless otherwise indicated. All data were analyzed using JMP10.0 MDSU statistical software (SAS Institute, Cary, NC, USA).

## Results

### *Characteristics of patients*

Among 7649 patients who underwent PCI, 69 patients (1.3%) who were below 40 years and 4225 patients (55.2%) who were above 65 years were identified as young adults and old adults, respectively. The baseline characteristics of these patients are shown in Tables 1 and 2. Young patients were predominantly men and the mean age was 36 years. Thirty percent of them were current smokers, and the mean BMI was 26.7 ± 5.0 kg/m$^2$. All patients had ≥1 conventional cardiovascular risk factor, and 75% of them had single vessel disease.

### *Univariate and multivariate analysis for the composite endpoint*

Outcome data were fully documented during the follow-up period (median 9.8 years, interquartile range: 3.9–18.8 years).

In young adults, during the follow-up period, 4 (5.8%) patients died (2 sudden death, 1 STEMI, 1 sepsis), and 6 (8.7%) suffered from ACS (3 STEMI, 1 NSTEMI, 2 UAP). In univariate analysis, current

**Table 1**
Baseline characteristics.

| | Young adults (age ≤40, $n$ = 69) | Old adults (age ≧65, $n$ = 4225) | $p$-Value |
|---|---|---|---|
| Age | 36.1 ± 4.9 | 73.1 ± 5.7 | <0.0001 |
| Male, $n$ (%) | 66 (95.7) | 3210 (75.7) | <0.0001 |
| Smoking, $n$ (%) | | | <0.0001 |
| Current smoker | 21 (30.5) | 671 (15.8) | |
| Former smoker | 31 (44.9) | 1925 (45.5) | |
| Never smoker | 17 (24.6) | 1629 (38.7) | |
| HT, $n$ (%) | 33 (47.8) | 3104 (73.2) | 0.003 |
| DM, $n$ (%) | 23 (33.3) | 1958 (46.2) | 0.32 |
| BMI | 26.7 ± 5.0 | 23.5 ± 3.3 | <0.0001 |
| LDL-C (mg/dl) | 127.9 ± 52.7 | 110.4 ± 31.9 | 0.02 |
| HDL-C (mg/dl) | 41.8 ± 20.8 | 42.6 ± 12.9 | 0.81 |
| TG (mg/dl) | 174.1 ± 89.7 | 120.3 ± 63.8 | <0.0001 |
| eGFR (ml/min/1.73 m$^2$) | 90.1 ± 21.6 | 61.4 ± 22.1 | <0.0001 |
| EF (%) | 59.1 ± 11.2 | 61.3 ± 13.7 | 0.41 |
| ACS, $n$ (%) | | | 0.34 |
| STEMI | 12 (17.4) | 666 (15.7) | |
| NSTEMI | 2 (2.9) | 55 (1.3) | |
| UAP | 8 (11.6) | 514 (12.8) | |
| Family history of CHD, $n$ (%) | 27 (40.9) | 1136 (26.7) | 0.03 |
| Vessel disease, $n$ (%) | | | <0.0001 |
| 1VD | 51 (75) | 1648 (38.7) | |
| 2VD | 13 (18) | 1364 (32.1) | |
| 3VD | 5 (7) | 1243 (29.2) | |

HT, hypertension; DM, diabetes mellitus; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; EF, ejection fraction; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UAP, unstable angina; CHD, coronary heart disease; VD, vessel disease.

**Table 2**
Use of medications (young adults) at discharge.

| | $n$ = 69 |
|---|---|
| Aspirin, $n$ (%) | 64 (92.9) |
| Antiplatelet drug, $n$ (%) | 47 (68.1) |
| ACE-I/ARB, $n$ (%) | 23 (34.8) |
| β-Blocker, $n$ (%) | 21 (31.8) |
| Calcium channel blocker, $n$ (%) | 31 (46.9) |
| Statin, $n$ (%) | 30 (45.5) |
| OHA, $n$ (%) | 6 (8.7) |
| Insulin, $n$ (%) | 3 (4.3) |

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; OHA, oral hypoglycemic agent.

smoking was identified as the only significant predictor of the composite endpoint (all-cause death and ACS) (Table 3). Survival curves of patients with and without current smoking are shown in Fig. 1. Multivariate Cox proportional hazards regression analysis revealed that current smoking was a significant independent predictor of the composite endpoint (HR 4.46, 95% CI 1.08–19.1, $p = 0.04$) (Table 3).

In older adults, univariate analysis revealed age, EF, use of statin, HDL-C, TG, and CKD were significant or borderline factors ($p < 0.10$) for the composite endpoint. Multivariate Cox proportional hazards regression analysis adjusted for these factors revealed that age and use of statins and EF were significant independent predictors of the composite endpoint (HR 1.05, 95% CI 1.03–1.07, $p < 0.0001$; HR 0.65, 95% CI 0.54–0.78, $p < 0.0001$; HR 0.98, 95% CI 0.97–0.99, $p < 0.0001$, respectively).

## Discussion

The important new finding of this study is that current smoking was a determinant of poor prognosis in young CHD patients (≤40 years old) who underwent PCI and young patients represented 1.3% of all who underwent PCI in our institution over a 26-year period. Previous reports indicated that the development of CHD in young adults is rare ranging from 1 to 10% [2,15–18]. In agreement with previous reports, the features of background in young patients of our study were higher prevalence of smokers and obesity, and three-quarters of patients had single-vessel disease. The prevalence of diabetes and hypertension was 33% and 48%, respectively. All patients had >1 conventional cardiovascular risk factors. The risk factors associated with atherosclerosis in young patients are similar to those in older patients, and nearly all young patients had at least one conventional cardiovascular risk factor [19]. Furthermore, although older patients had higher rates of diabetes and hypertension, younger patients showed higher rates of smoking and obesity [20].

There are only a few previous reports that evaluated long-term outcomes of young patients following PCI. Rallidis and colleagues found that smoking was the most powerful predictor for recurrence of cardiac events in young AMI patients (age ≦35 years) [21]. Cole and colleagues found that DM, active smoking, and left ventricular systolic dysfunction were predictors of increased mortality in young patients (≤40 years) with CHD [11]. In their study, the number of subjects was large (843 patients ≤40 years with CHD) and the subjects were followed for 15 years. However, the baseline data were collected from 1975 to 1985 and revascularization was performed in only 60% (27% underwent PCI and 34% underwent coronary artery bypass surgery). Therefore, these results might have been different from current results, which were derived from current medical and revascularization practice of CHD treatment. More recently, Meliga and colleagues found that active smoking and a left ventricular ejection fraction <50% were independent predictors of major adverse cardiac and cerebrovascular events in young patients (≤40 years) who underwent PCI [22]. The subjects in their study were similar to those in our study in terms of patient characteristics. Although a greater number of patients (214 patients ≤40 years) underwent PCI in their study, the follow-up duration was much shorter (median 757 days) compared with the present study. Furthermore, there are no previous studies of PCI in young patients in a Japanese population. Thus, our study is the first to evaluate the long-term outcomes of PCI in young Japanese patients.

In general, patients with CHD usually have one or more traditional risk factors (e.g. hypertension, DM, dyslipidemia, obesity, smoking, family history of CHD). This is true even in young CHD patients and these patients often have multiple traditional CHD risk factors. It was reported that young CHD patients were likely to be smokers, men, obese and to have a positive family history of CHD [10]. However, young patients are more likely to have less extensive coronary atherosclerotic lesion (i.e. single-vessel disease) and less complex CAD than elderly patients [5]. Indeed, in the present study, 75% of patients had single-vessel disease. Azegami and colleagues compared the clinical characteristics of young (≤40 years) and old (≥50 years) Japanese CHD patients who were diagnosed with CHD between 1992 and 2002 [8]. In their study, young CHD patients were more likely to be men, obese, smokers, and to have hyperlipidemia. Similarly, patients in our study were obese (BMI 26.7 ± 5.0) and likely to be smokers.

The presence of multiple coronary risk factors in young CHD patients may play important roles in the secondary prevention of CHD. In the present study, current smoking was the only independent predictor of long-term outcome. There were three other studies in which the predictors of morbidity and mortality in young patients with CHD were assessed [11,21,22]. Although the independent predictors of outcomes appear to vary across studies, including ours, these differences are probably due to differences in the characteristics of the study populations. However, smoking was a consistent predictor of major adverse events in all studies.

Smoking may increase the risk of incident adverse events through the activation of the inflammatory cascade and endothelial dysfunction [23–25]. Zieske and colleagues found smoking was strongly associated with presence of advanced atherosclerosis [26]. Furthermore, Burke and colleagues demonstrated that smoking is associated with coronary thrombosis in both young men [27] and

**Table 3**
Cox proportional hazards model for the predictors of the composite endpoint.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p | HR | 95% CI | p |
| Age | 1.02 | 0.92–1.17 | 0.78 | 1.01 | 0.89–1.21 | 0.95 |
| Gender (F/M) | 1.34 | 0.07–7.04 | 0.79 | 3.91 | 0.20–26.1 | 0.29 |
| BMI | 1.06 | 0.95–1.16 | 0.29 | 1.04 | 0.93–1.15 | 0.47 |
| HT | 1.87 | 0.59–6.37 | 0.28 | | – | |
| DM | 1.68 | 0.49–5.27 | 0.38 | | – | |
| Metabolic syndrome | 1.51 | 0.41–5.47 | 0.52 | | – | |
| LDL-C | 0.99 | 0.98–1.01 | 0.37 | | – | |
| HDL-C | 0.99 | 0.96–1.02 | 0.97 | | – | |
| TG | 1.01 | 0.99–1.02 | 0.71 | | – | |
| Current smoker | 3.79 | 1.05–13.1 | 0.04 | 4.46 | 1.08–19.1 | 0.04 |
| Family history of CHD | 1.24 | 0.38–4.64 | 0.72 | | – | |
| CKD | 1.72 | 0.10–13.3 | 0.66 | | – | |
| OMI | 2.02 | 0.40–9.17 | 0.37 | | – | |
| EF | 0.99 | 0.93–1.06 | 0.72 | | – | |

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CHD, coronary heart disease; CKD, chronic kidney disease; OMI, old myocardial infarction; EF, ejection fraction.

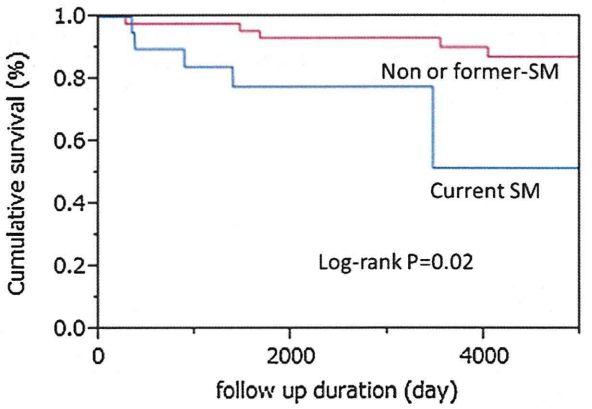


**Fig. 1.** Kaplan–Meier curve for the composite endpoint of all-cause death or acute coronary syndrome. Current smokers had a significantly worse outcome compared with non- or former smokers (log-rank test; $p = 0.02$). SM, smoker.

women [28]. The results of these studies and ours show the impact of smoking on clinical outcomes in young CHD patients, and emphasize the importance of smoking cessation in young adults [29], even in those without other CHD risk factors.

Our study is subject to some limitations. First, the number of subjects was limited and PCI was performed at a single center. Second, the present study was observational in nature. Although we adjusted our Cox proportional hazards model for known confounding variables, other unknown confounders might have affected the outcome.

## Conclusions

In conclusion, current smoking and obesity (high BMI) are the important clinical characteristics in young Japanese CHD patients who undergo PCI. Although the long-term prognosis of young Japanese CHD patients is acceptable, current smoking is a significant independent predictor of death and the recurrence of ACS in young Japanese CHD patients who are obese.

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