levels and changes in peak VO_2 in CR participants with DM after coronary events [7]. Park et al. reported that a low level of muscle strength was a predictor of physical limitation, and diabetes was associated with a low level of skeletal muscle strength and deterioration in quality [8]. We recently reported that muscle strength and exercise tolerance were significantly lower in DM patients than non-DM patients at the beginning of CR after CABG [9]. However, the effects of CR on muscle mass, muscle strength, and exercise tolerance in DM patients undergoing CR after CABG has not been fully elucidated. The aim of this study was to investigate the effects of CR on muscle mass, muscle strength, and exercise tolerance in DM patients who received CR after CABG.

Methods

Subjects

We enrolled 78 consecutive patients who completed a supervised CR for 6 months after CABG at Juntendo University Hospital from July 2002 to February 2005. The patients were divided into 2 groups: those with DM (DM group, $n=37$) and those without DM (non-DM group, $n=41$), according to the guidelines of the Japan Diabetes Society (JDS), which includes history of medical treatment, fasting plasma glucose $\geq$ 126 mg/dl or casual plasma glucose $\geq$ 200 mg/dl, and hemoglobin (Hb) A1c $\geq$ 6.1% [10]. All patients participated in the CR program 6–8 days after CABG. All subjects gave written informed consent and the ethical committee of the institution approved this study.

Rehabilitation protocol

The CR program consisting of warm-up stretching, aerobic exercise, resistance training, and cool-down, was scheduled once or twice a week for 6 months, as described previously [11,12]. Aerobic exercise consisted of a cycle ergometer, treadmill, and walking on an indoor track with a total duration of approximately 60 min exercise intensity was prescribed individually at the anaerobic threshold (AT) level, as measured by an ergometer test using expiratory gas analysis or a rating of 11–13 on a standard Borg's perceived exertion scale. Resistance training, which was gradually added to the exercise program at least 6 weeks after participation, included sit-ups, back kicks and front raises, squats, and push-ups, using the patient's own weight. This training consisted of 1–2 sets of 10–15 repetitions for each muscle group with 3–5 min rest between sets. Patients were encouraged to perform home-based aerobic exercise twice a week for more than 20 min at a rating of 11–13 of perceived exertion on Borg's scale. All subjects were instructed to follow the phase II diet of the American Heart Association at the beginning of CR. An educational program regarding CAD and its risk factors at baseline was also provided for each subject by physicians, nurses, and dietitians.

Measurements

We assessed body composition, muscle strength, and exercise tolerance at the beginning and end of CR. Anthropometric parameters were assessed using body mass index (BMI), waist size, thigh circumference, triceps skin fold thickness measured on the dominant hand, and mid-upper arm circumference. Thigh circumference was measured directly below the gluteal fold of the right thigh according to WHO standards [13]. Mid-upper arm muscle area (MAMA) was calculated according to a standard method [14]. The percentages of body fat and lean body weight were measured by BOD POD® (Life Measurement, Inc., Concord, CA, USA), as described previously [11,12]. The power of the thigh muscles was measured using the Cybex770 system (Cybex Division of Lumex, Ronkonkoma, NY, USA), as also reported previously [11,12]. The isokinetic peak torques of the knee extensor (Ext) and flexor (Flex) muscles were measured at 60°/s, and those were adjusted by body weight according to the following formula: strength (Nm) $\times$ 100/kg body weight. Handgrip power (HGP) in the dominant hand was also measured. To measure peak oxygen consumption (peak VO_2) and oxygen uptake at the AT, patients underwent ergometer testing (Corival 400, Lobe B.V., Groningen, Netherlands) using an expiratory gas analysis machine (Vmax-295, SensorMedics Co., Yorba Linda, CA, USA). After a period of resting, warm-up was performed for a few minutes at 20 W, followed by ramp loading (15 W/min) until subjective exhaustion, progressive angina, ST-segment depression ($\geq$2 mm), or sustained tachyarrhythmia. The point of AT was determined by the "V-slope" method.

Statistical analyses

The results are expressed as mean $\pm$ standard deviation and were analyzed using the StatView software (Version 5.0J for Windows, SAS Institute, Cary, NC, USA). Comparisons between the DM and non-DM groups were performed by Student's *t*-test. Data at baseline and after 6 months of CR were compared for each patient by paired *t*-test to evaluate the singular effects of CR. Correlation coefficients were determined by linear regression analysis. Statistical significance of correlation coefficients was determined by the method of Fisher and Yates. A *p*-value of less than 0.05 was considered significant.

Results

Characteristics of CR subjects

The clinical characteristics of the subjects are presented in Table 1. Thirty-seven patients were diagnosed as having DM. No significant differences with regard to age, gender, coronary risk factors, number of diseased vessels, ejection fraction, or physiological variables, were observed between the DM and non-DM groups. Thirty-six patients received complete revascularization using the off-pump operation. One patient who had received re-CABG was in the DM group. No significant differences in the concomitant use of drugs, including antiplatelets, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or statins, were observed between the two groups. In the DM group, 24 patients (65%) and 13 patients (35%)

Table 1
Clinical characteristics of the study subjects.

	DM	Non-DM	*p*-Value
N	37	41	
Age (year)	63.5 ± 10	64.1 ± 9	NS
Male (%)	29 (78)	39 (95)	NS
Hypertension (%)	22 (61)	30 (73)	NS
Dyslipidemia (%)	28 (76)	31 (76)	NS
Current smoker (%)	17 (49)	21 (53)	NS
Familial history (%)	11 (26)	9 (26)	NS
History of MI (%)	2 (5)	0 (0)	NS
History of PCI (%)	2 (5)	0 (0)	NS
History of previous CABG (%)	1 (3)	0 (0)	NS
Diseased vessels			
LMT (%)	9 (25)	2 (5)	NS
3VD (%)	18 (48)	28 (68)	NS
1–2VD (%)	10 (27)	11 (27)	NS
Ejection fraction (%)	59.7 ± 16	65.3 ± 12	NS
Off-pump CABG (%)	36 (97)	41 (100)	NS
Exercise in hospital (times)	16 ± 14	18 ± 14	NS

Data are presented as the mean value ± SD. DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary arterial bypass grafting; LMT, left main trunk; VD, vessel disease.

were treated with oral anti-diabetic agents and insulin, respectively. No significant differences were observed between the two groups in exercise duration in the CR program (data not shown). No subject in either group showed any worsening of symptoms or had cardiovascular events during the 6 months of the study.

Serum lipid profiles and glucose parameters

Serum lipid profiles and glucose parameters at baseline and the end of CR are presented in Table 2. Fasting blood glucose and HbA1c levels before and after CR were significantly higher in the DM group than in the non-DM group (both $p < 0.05$). Lipid profiles were not significantly different between the two groups at both baseline and the end of CR.

Anthropometric parameters

The anthropometric parameters at baseline and after CR in both groups are presented in Table 3. The anthropometric parameters at baseline were not significantly different between the two groups. In the non-DM group, waist circumference (from 84.5 ± 7.8 to 82.2 ± 6.7 cm, $p < 0.05$) was significantly decreased, and thigh circumference (from 48.9 ± 4.1 to 50.7 ± 3.7 cm, $p < 0.05$), arm forced circumference (from 29.0 ± 2.6 to 30.0 ± 2.4 cm, $p < 0.05$), mid-upper arm muscle circumference (from 25.7 ± 2.5 to 26.5 ± 2.4 cm, $p < 0.05$), and MAMA (from 53.2 ± 10.3 to 56.5 ± 10.0 cm^2, $p < 0.05$) were significantly increased. In the DM group, waist circumference (from 83.4 ± 8.3 to 80.2 ± 5.7 cm, $p < 0.05$) was significantly decreased, however, thigh circumference, arm forced circumference, mid-upper arm muscle circumference, and MAMA were not significantly altered. At the end of CR, thigh circumference (47.3 ± 2.5 cm vs. 50.7 ± 3.7 cm, $p < 0.05$), arm forced circumference, (28.4 ± 1.6 cm vs. 30.0 ± 2.4 cm, $p < 0.05$), mid-upper arm muscle circumference (25.0 ± 1.8 cm vs. 26.5 ± 2.4 cm, $p < 0.05$), and MAMA (49.9 ± 7.1 cm^2 vs. 56.5 ± 10.0 cm^2, $p < 0.05$) were significantly lower in the DM group than in the non-DM group.

Exercise tolerance and muscle strength

Exercise tolerance and muscle strength at baseline and after CR in each group are presented in Table 4. At the beginning of CR, the levels of peak VO_2 (13.7 ± 4.0 ml kg^{-1} min^{-1} vs. 16.0 ± 4.7 ml kg^{-1} min^{-1}, $p < 0.05$) and thigh muscle strength (136.3 ± 42.7 Nm kg^{-1} × 100 vs. 162.7 ± 47.9 Nm kg^{-1} × 100, $p < 0.05$) were significantly lower in the DM group than in the non-DM group. No significant differences in HGP (28 ± 9 kg vs. 31 ± 9 kg, NS) were observed between the two groups. At the end of CR, both groups showed significant improvements in exercise tolerance and muscle strength. Improvements in exercise tolerance and muscle strength were identical in the DM and non-DM groups. However, the levels of peak VO_2 (19.4 ± 3.8 ml kg^{-1} min^{-1} vs. 22.9 ± 5.4 ml kg^{-1} min^{-1}, $p < 0.05$) and AT (11.3 ± 2.2 ml kg^{-1} min^{-1} vs. 13.3 ± 3.4 ml kg^{-1} min^{-1}, $p < 0.05$) were still significantly lower in the DM group than in the non-DM group. The levels of thigh Ext muscle strength (164.1 ± 43.3 Nm kg^{-1} × 100 vs. 193.3 ± 51.9 Nm kg^{-1} × 100, $p < 0.05$) and HGP (30 ± 7 kg vs. 35 ± 8 kg, $p < 0.05$) were also significantly lower in the DM group than in the non-DM group.

Correlations between muscle mass, muscle strength, and HbA1c

At the end of CR, the values for thigh muscle strength were correlated with thigh circumference ($r = 0.44$, $p < 0.01$) and MAMA ($r = 0.37$, $p < 0.05$) (Fig. 1). The values of HGP were correlated with thigh circumference ($r = 0.52$, $p < 0.01$), and MAMA ($r = 0.48$, $p < 0.05$) (Fig. 1). The same trends were observed at the beginning of CR [9]. Moreover, the percent change in Ex muscle strength was

Table 2
Comparison of glucose, lipid, and other parameters between the DM and non-DM groups.

	DM group ($n = 37$)		Non-DM group ($n = 41$)	
	Baseline	After	Baseline	After
Fasting blood glucose (mg/dl)	143 ± 57	167 ± 68	103 ± 14	112 ± 20
HbA1c (%) (JDS)	7.0 ± 1.3	7.2 ± 1.4	5.1 ± 0.4	5.2 ± 0.5
LDL-C (mg/dl)	116 ± 37	97 ± 22	124 ± 40	89 ± 16
HDL-C (mg/dl)	48 ± 15	50 ± 14	51 ± 12	49 ± 12
TG (mg/dl)	161 ± 97	168 ± 191	149 ± 66	158 ± 97
Creatinine (mg/dl)	1.4 ± 2.3	1.1 ± 1.3	0.8 ± 0.2	0.8 ± 0.2
CRP (mg/dl)	0.6 ± 1.4	0.6 ± 1.3	0.2 ± 0.2	0.7 ± 2.0

Data are presented as the mean value ± SD. DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CRP, C-reactive protein.
$^{*}p < 0.05$ compared with at baseline.
$^{**}p < 0.05$ compared with the DM group at baseline.
$^{\#}p < 0.05$ compared with the DM group after 6 months.

Table 3
Comparison of anthropometric parameters between the DM and non-DM groups.

	DM group ($n = 37$)		Non-DM group ($n = 41$)	
	Baseline	After	Baseline	After
Body mass index (kg m^{-2})	23.3 ± 2.7	22.6 ± 1.9	23.4 ± 2.9	23.7 ± 2.5
Lean body weight (kg)	48.4 ± 9.8	45.2 ± 5.2	49.4 ± 7.7	49.6 ± 7.3
Waist circumference (cm)	83.4 ± 8.3	80.2 ± 5.7*	84.5 ± 7.8	82.2 ± 6.7*
Thigh circumference (cm)	47.2 ± 4.3	47.3 ± 2.5	48.9 ± 4.1	50.7 ± 3.7$^{*,\#}$
Arm forced circumference (cm)	28.3 ± 2.7	28.4 ± 1.6	29.0 ± 2.6	30.0 ± 2.4$^{*,\#}$
Mid-upper arm muscle circumference (cm)	24.9 ± 2.4	25.0 ± 1.8	25.7 ± 2.5	26.5 ± 2.4$^{*,\#}$
Mid-upper arm muscle area (cm^2)	49.7 ± 9.5	49.9 ± 7.1	53.2 ± 10.3	56.5 ± 10.0$^{*,\#}$

Data are presented as the mean value ± SD. DM, diabetes mellitus.
* $p < 0.05$ compared with at baseline.
$^{\#}$ $p < 0.05$ compared with the DM group after 6 months.

Table 4
Comparison of exercise tolerance and muscle strength between the DM and non-DM groups.

	DM group ($n=37$)		Non-DM group ($n=41$)	
	Baseline	After	Baseline	After
Anaerobic threshold (ml kg^{-1} min^{-1})	8.3 ± 1.6	11.3 ± 2.2*	9.7 ± 2.7	13.3 ± 3.4$^{*,\#}$
Peak VO_2 (ml kg^{-1} min^{-1})	13.7 ± 4.0	19.4 ± 3.8*	16.0 ± 4.7**	22.9 ± 5.4$^{*,\#}$
Anaerobic threshold workload (W)	34 ± 15	52 ± 21*	39 ± 20	66 ± 22$^{*,\#}$
Peak workload (W)	73 ± 23	107 ± 21*	81 ± 29	124 ± 29$^{*,\#}$
Knee extension (Nm kg^{-1} × 100)	136.3 ± 42.7	164.1 ± 43.3*	162.7 ± 47.9**	193.3 ± 51.9$^{*,\#}$
Knee flexion (Nm kg^{-1} × 100)	80.0 ± 26.7	102.4 ± 30.3*	91.2 ± 29.2	115.1 ± 30.7*
Power of hand grip (kg)	28 ± 9	30 ± 7*	31 ± 9	35 ± 8$^{*,\#}$

Data are presented as the mean value ± SD. DM, diabetes mellitus.
* $p<0.05$ compared with at baseline.
** $p<0.05$ compared with the DM group at baseline.
$^{\#}$ $p<0.05$ compared with the DM group after 6 months.

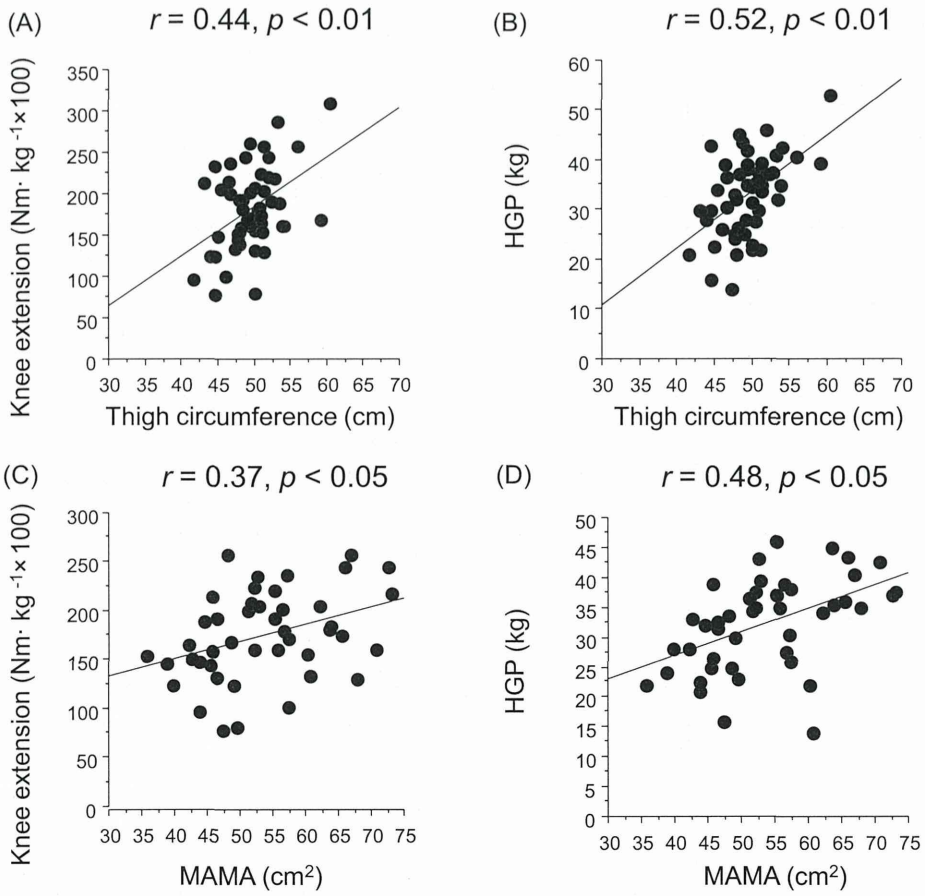

Fig. 1. Correlations between muscle strength and muscle mass. At the end of cardiac rehabilitation, the levels of muscle strength of thigh were correlated with thigh circumference ($r=0.44$, $p<0.01$) (A) and MAMA ($r=0.37$, $p<0.05$) (C). The values of HGP were correlated with thigh circumference ($r=0.52$, $p<0.01$) (B), and MAMA ($r=0.48$, $p<0.05$) (D). MAMA, mid-upper arm muscle area; HGP, hand grip power.

correlated with MAMA ($r=0.47$, $p<0.005$) and HbA1c ($r=-0.41$, $p<0.05$) (Fig. 2).

Discussion

In the present study, we demonstrated that: (1) the levels of muscle strength and exercise tolerance at the beginning and end of CR were significantly lower in the DM group than in the non-DM group; (2) exercise tolerance and muscle strength after CR were significantly improved in both groups; (3) muscle mass was significantly increased after CR in the non-DM group, but not in the DM group; and (4) percent change in muscle strength was correlated with that of HbA1c in patients undergoing CR after CABG. Our group and others previously reported a relationship between muscle strength and peak VO_2 in patients with cardiovascular disease [15,16]. However, to the best of our knowledge, this is the first report to simultaneously demonstrate the effects of CR on muscle mass, muscle strength, and exercise tolerance, and to compare DM and non-DM patients undergoing CR after CABG.

CR is described as a class I recommendation in most contemporary cardiovascular clinical practice guidelines. Following CR, patients show increased exercise tolerance and muscle strength, which have proven to be the strongest predictors of the risk of death among subjects both with and without known cardiovascular disease [17,18]. Boulé et al. reported in a meta-analysis that

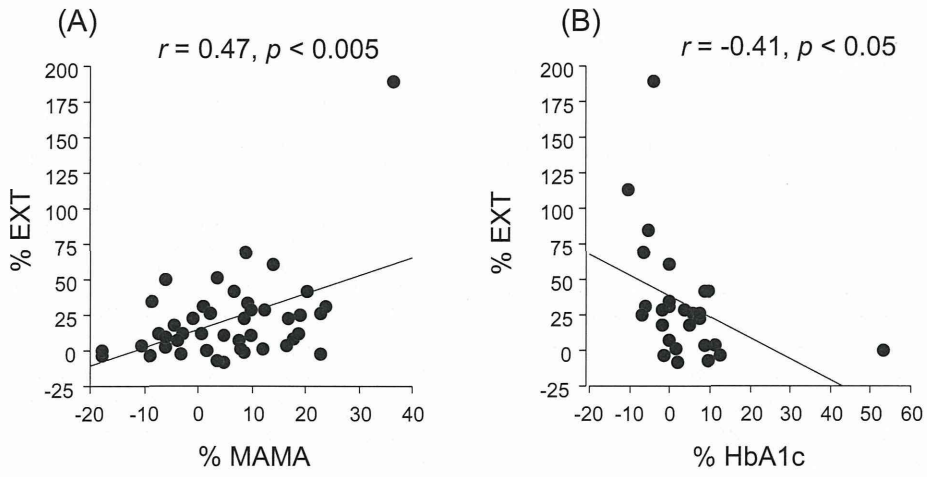

Fig. 2. Correlations between percent change in muscle strength and those in MAMA and HbA1c. A significant relation between the percent change in the muscle strength and those in MAMA was observed ($r = 0.47$, $p < 0.005$) (A). A significant inverse relation between the percent change in the muscle strength and those in HbA_1c was observed ($r = -0.41$, $p < 0.05$) (B). % EXT, percent change of knee extension; % MAMA, percent change of mid-upper arm muscle area; % HbA_1c, percent change of hemoglobin A_1c.

structured exercise training in DM patients achieved an 11.8% increase in peak VO_2 [19]. This is particularly important, because an improvement in peak VO_2 of 1.44 ml kg^{-1} min^{-1} was equivalent to a 7.9% reduction in overall mortality [20]. Moreover, exercise has many potential benefits, including not only improving exercise tolerance, but also improving glucose metabolism, insulin signaling, lipid profile, endothelial function, and blood pressure, reducing vascular inflammation and facilitating weight maintenance [7]. Either aerobic or resistance training alone improves glycemic control in DM patients, however, a combination of both may be more beneficial for improving risk factors than each alone [18]. Williams et al. have reported a combination of aerobic and resistance training exercise improved through neuromuscular adaptation, muscle fiber hypertrophy, and increased muscle oxidative capacity [21]. A previous study demonstrated the beneficial effects of resistance training on muscle mass and strength in chronic heart failure [18]. We also reported that CR with aerobic and resistance training had beneficial effects not only on the modification of metabolic risk factors, but also on improvement in exercise tolerance and muscular strength in patients with metabolic syndrome following CABG [12].

Levels of exercise tolerance and muscle strength were lower in DM than in non-DM patients in the present study. A previous report showed that endothelial dysfunction associated with high glucose levels is caused by the increased production of vasoconstrictor prostanoids as a consequence of protein kinase C activation [22]. Other studies have demonstrated that DM patients have impaired metabolism of both glucose and fatty acids in skeletal muscles. In addition, the bioenergetic capacity of skeletal muscle mitochondria was found to be impaired in DM patients [23]. We previously observed a significant inverse relationship between fasting glucose levels and thigh muscle strength at the beginning of CR in DM patients after CABG [9].

The DM group showed no increase in muscle mass such as MAMA and thigh circumference (Table 3), both of which correlated with thigh muscle strength and HGP (Fig. 1). Vergès et al. reported that the effects of CR on exercise capacity were significantly lower in DM than in non-DM patients, and the response to CR was influenced by blood glucose levels [7]. Moreover, we showed a significant inverse relationship between percent change for HbA1c and that for thigh muscle strength in the DM group (Fig. 2). Park et al. demonstrated that functional muscle quality was relatively low in DM patients. Furthermore, long duration of diabetes and poor glycemic control were associated with deterioration in muscle quality. Diabetes with poor glycemic control is related to the presence and severity of peripheral neuropathy and inflammatory cytokines, which have detrimental effects on muscle function [8]. Chronic hyperglycemia induces a condition of oxidative stress that is causally involved in the development of skeletal muscle depletion [24]. The increased production of reactive oxygen species induced by hyperglycemia has also been suggested to be involved in the redox regulation of glucose transport in skeletal muscle [25]. Hyperglycemia leads to the production of Amadori products between glucose and reactive amino groups of serum proteins [26]. These products undergo further irreversible reactions to form advanced glycation end products that promote insulin resistance and trigger inflammation, which leads to diabetic vascular complications [26]. The DM group had 11.0 ± 6.7 years' duration of DM history in the present study, and the prevalence of microvascular complications, including retinopathy, nephropathy, and neuropathy was 38%. These data may explain the mechanisms by which improvements in muscle mass and strength, and exercise tolerance, were impaired in the DM group. Thus, not only exercise but also glycemic control may be important in improving muscle structure.

Several studies have shown a U-shaped association between BMI and mortality. Increased risk was independent of abdominal and general obesity, and lifestyle and cardiovascular risk factors such as blood pressure and lipid levels were related to early cardiovascular morbidity and mortality. Additionally, Heitmann et al. reported that this risk was related more to thigh than waist circumference [13]. A study in a cohort of community-dwelling Japanese elderly demonstrated that low arm muscle area was an independent risk factor for 2-year mortality [27]. We would like to clarify whether arm muscle area after CR can predict morbidity and mortality in DM patients after CABG.

There are some limitations to the present study. First, because this was a single-center study with a small sample size, studies of larger sample size are required to confirm these findings. Second, the exercise session at the outpatient clinic was encouraged once a week with at least 2 exercise sessions at home. However, while the mean number of CR sessions in hospital was 16–18 times, we have no data regarding home-based exercise frequency and intensity for either group, and we need to assess the effects of exercise frequency and intensity in a future study. The program used in this study may not have been sufficiently rigorous to alter parameters such as glucose control and lipid profiles. Third, we enrolled patients undergoing CR after CABG. Therefore, the results may not necessarily be representative of all DM patients with CAD. In a future study,

we need to investigate DM patients undergoing percutaneous intervention and/or those with acute coronary syndrome. Finally, we need to investigate whether different treatments, including intensive glucose control and a combination of aerobic and resistance training, can enhance muscle mass and ameliorate future cardiovascular events and long-term mortality in DM patients after CABG.

Conclusions

Patients with DM had lower muscle strength and lower exercise tolerance than non-DM patients at the beginning of CR after CABG. Both groups showed improved exercise tolerance and muscle strength after undergoing CR. However, DM patients had lower muscle mass, lower muscle strength, and lower exercise tolerance than non-DM patients at the end of CR. Moreover, improvement in muscle strength may be influenced by changes in muscle mass and high glucose levels in DM patients. Further studies are needed to assess whether a CR program including muscle mass intervention and aggressive glucose control would improve muscle mass and ameliorate future cardiovascular events in DM patients after CABG.

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ORIGINAL ARTICLE

Mortality risk of triglyceride levels in patients with coronary artery disease

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ABSTRACT

Objective The association between triglyceride level and the risk of coronary artery disease (CAD) remains controversial. In particular, the prognostic significance of triglyceride levels in established CAD is unclear. We aimed to assess the relationship between triglyceride levels and long-term (>10 years) prognosis in a cohort of patients after complete coronary revascularisation.

Design Observational cohort study.

Setting Departments of cardiology and cardiovascular surgery in a university hospital.

Patients Consecutive patients who had undergone complete revascularisation between 1984 and 1992. All patients were categorised according to the quintiles of fasting triglyceride levels at baseline.

Main outcome measures The risk of fasting triglyceride levels for all-cause and cardiac mortality was assessed by multivariable Cox proportional hazards regression analyses.

Results Data from 1836 eligible patients were assessed. There were 412 (22.4%) all-cause deaths and 131 (7.2%) cardiac deaths during a median follow-up of 10.5 years. Multivariable analyses including total and high-density lipoprotein cholesterol and other covariates revealed no significant differences in linear trends for all-cause mortality according to the quintiles of triglyceride (p for trend=0.711). However, the HR increased with the triglyceride levels in a significant and dose-dependent manner for cardiac mortality (p for trend=0.031). Multivariable analysis therefore showed a significant relationship between triglyceride levels, when treated as a natural logarithm-transformed continuous variable, and increased cardiac mortality (HR 1.51, p=0.044).

Conclusions Elevated fasting triglyceride level is associated with increased risk of cardiac death after complete coronary revascularisation.

Several epidemiological studies have investigated the relationships between serum triglyceride levels and morbidity and mortality rates of coronary artery disease (CAD).[1–4] However, the evidence for elevated triglyceride levels as an independent risk factor for CAD remains controversial because there is no uniformity in data obtained in large epidemiological studies. There is a concern that adjustment for other abnormal lipid profiles, such as high-density lipoprotein (HDL) cholesterol levels, attenuates the relationship between triglycerides and CAD because there is an inverse correlation between triglyceride levels and HDL cholesterol levels. Nevertheless, meta-analyses have shown that serum triglyceride levels are an independent risk factor for morbidity and mortality rates of CAD in primary prevention.[5–8]

Unlike primary prevention, there are few data on the long-term prognostic significance of triglyceride levels in secondary prevention of CAD. The relationship between triglyceride levels and mortality risk after complete coronary revascularisation has not been established. We aimed to assess the relationship between triglyceride levels and long-term prognosis in a cohort of patients with CAD after complete coronary revascularisation.

METHODS

Subjects

We analysed data from consecutive patients who had undergone coronary revascularisation, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), at Juntendo University Hospital (Tokyo, Japan) between January 1984 and December 1992. We included patients who had achieved complete revascularisation—that is, patients in whom no unbypassed major vessels had a stenosis of ≥50%.[9 10] Patients with an untreated neoplasm at baseline and those with associated complex cardiac procedures such as valve replacement or aneurysm repair at the time of surgical revascularisation were excluded. The study was approved by the institute's internal review board and was performed according to the principles expressed in the Declaration of Helsinki and the ethics policy of the institute.

Data collection and definitions of variables

Demographic data including age, gender, body mass index (BMI), coronary risk factors, medication use, revascularisation procedure-related factors and comorbidities were prospectively collected. Blood samples were obtained in the early morning after an overnight fast. Hypertension was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg or treatment with antihypertensive medications. Diabetes mellitus (DM) was defined as fasting plasma glucose level of ≥6.99 mmol/l or treatment with oral hypoglycaemic drugs or insulin injections. A current smoker was defined as a patient who smoked at the time of complete revascularisation or who had quit smoking within 1 year prior to the procedure. Patients with isolated PCI had achieved complete revascularisation by PCI without bypass grafting.

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Outcomes

The follow-up period ended on 30 September 2000. Survival data were collected by establishing serial contact with the patients or their families or from the medical records of deceased patients or those who continued to be followed up at our hospital. Information about the circumstances and date of death was obtained from the families of patients in cases where the patient died at home, and details of the events or the cause of death was supplied by other hospitals or clinics where the patients were admitted. Mortality data were categorised according to the causes of death (eg, all-cause or cardiac deaths) using the International Classification of Diseases, Ninth Revision codes 410–414, 785.51 and 798.

Statistical analysis

For the main analysis, all patients were categorised according to the quintiles of triglyceride levels. Continuous variables are expressed as mean±SD and categorical data are tabulated as frequencies and ratios. Differences between the baseline characteristics of patients within each triglyceride category were analysed by analysis of variance for continuous variables and the Cochrane–Armitage test for trend for proportions. To determine whether the results differed with the cut-off points, we performed secondary analyses in which triglyceride levels were treated as a natural logarithm-transformed continuous variable.

Cumulative mortalities were plotted using Kaplan–Meier curves and differences between quintiles of triglyceride levels were determined using log-rank tests. p Values for log-rank trend tests were also estimated. Cox proportional hazard models were used to compute HR and 95% CI for each quintile of triglyceride level using the lowest quintile as the reference group. Linear trend analyses were performed by using linear contrast coefficients (−2, −1, 0, 1, 2) in Cox proportional hazard models. The assumption of proportional hazards was assessed using a log-minus-log survival graph. Models were initially adjusted for age and gender (Model 1). To determine the role of triglycerides independent of other lipid markers, we adjusted the models for total and HDL cholesterol levels (Model 2). Furthermore, multivariable models were adjusted for non-HDL and HDL cholesterol levels (Model 3) and for BMI, presence of hypertension, presence of DM, current smoking, family history of CAD, prior myocardial infarction (MI), prior stroke, presence of atrial fibrillation, under dialysis, left ventricular ejection fraction, number of diseased vessels, presence of an arterial bypass to left anterior descending artery, presence of a left main trunk lesion, whether complete revascularisation was achieved by isolated PCI and use of drugs (aspirin, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, statins, fibrates and niacin) in addition to the variables used in Model 2 (Model 4). To avoid overadjustment, the latter covariates were added only if they were significant predictors of death from all-cause or cardiac death at an α level of 0.1. Finally, multivariable models were further adjusted for non-HDL cholesterol levels plus the same variables as in Model 4 other than total cholesterol (Model 5).

To assess the potential heterogeneity of the effect of triglyceride levels on cardiac mortality we performed subgroup analyses. The subgroups included age groups (cut-off 60 years), gender, presence/absence of DM, total cholesterol (cut-off 5.69 mmol/l), HDL cholesterol (cut-off 1.29 mmol/l) and use of statins. The first-order interactions in multivariable Cox proportional hazards models were examined by entering interaction terms between triglyceride levels and the abovementioned subgroup variables. We also determined the effect of triglyceride levels on cardiac mortality in each subgroup.

A p value of <0.05 was considered statistically significant unless indicated otherwise. All data were analysed using SAS V.9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

We assessed data from 1836 eligible patients who had undergone complete coronary revascularisation during the study period. Baseline and clinical event data were fully documented during a median follow-up period of 10.5 years. All patients underwent PCI with simple balloon angioplasty; no patient received stent implantation since stents were not available when complete revascularisation was achieved. All CABG procedures were performed using a conventional cardiopulmonary bypass; arterial grafts were used in 51.4% of cases. None of the patients had type 1 DM. During the follow-up period 412 patients (22.4%) died from any cause and 131 patients (7.2%) died from cardiac causes.

The baseline characteristics of patients by quintiles of triglyceride levels are shown in table 1. Patients with high triglyceride levels were likely to be young, male and current smokers with a high BMI and total cholesterol level, a low HDL cholesterol level and frequently had prior MI. Among patients with high triglyceride levels, a smaller percentage of patients underwent revascularisation by isolated PCI, a high percentage were taking aspirin and a low percentage were taking statins.

The cumulative survival curves of patients according to the quintiles of triglyceride levels are shown in figure 1. Patients with high triglyceride levels were more likely to have high cumulative cardiac mortality rates (figure 1B) but they did not show any trend to high cumulative all-cause mortality (figure 1A).

The results of Cox proportional hazard regression analyses for all-cause and cardiac mortality are summarised in figure 2. Linear trends for all-cause mortality according to the quintiles of triglyceride levels were not significant in any models except for Model 1. However, among each quintile of triglyceride level in all models, HR increased significantly with the triglyceride levels in a dose-dependent manner for cardiac mortality.

The results of Cox proportional hazard regression analyses, in which triglyceride levels were treated as natural logarithm-transformed continuous variables, are also shown in figure 2. For all-cause mortality, only Model 1 showed a significant association between logarithm-transformed triglyceride level and mortality. However, for cardiac mortality, all models showed significant associations between these two factors.

We also conducted a subgroup analysis separately from the age, gender, presence of DM, total and HDL cholesterol levels and the use of statins for all-cause and cardiac death. Although associations of triglyceride level with mortality were more prominent in men, patients with low HDL and patients not receiving statins, all p values for interaction were not significant (figure 3).

DISCUSSION

In this study we made several important findings that provide insights into the relationship between triglyceride levels and cardiovascular diseases. First, we found that patients in the highest triglyceride quintile had a significantly greater risk of cardiac mortality than those in the lowest triglyceride quintile. Further, HR increased with the triglyceride quintile in a significant and dose-dependent manner, and high logarithm-transformed triglyceride levels were associated with increased long-term cardiac

Table 1 Baseline characteristics

	Triglyceride quintile, mmol/l					
	Q1 (≤1.11) N=369	Q2 (1.12–1.46) N=359	Q3 (1.47–1.83) N=369	Q4 (1.84–2.45) N=370	Q5 (≥2.46) N=369	p Value*
Age, years	60±9	61±9	59±8	58±9	58±8	<0.001
Men, n (%)	297 (81)	296 (82)	309 (84)	324 (88)	336 (91)	<0.001
BMI, kg/m^2	23±3	23±3	24±3	24±3	24±2	<0.001
Diabetes mellitus, n (%)	149 (40)	136 (38)	132 (36)	137 (37)	149 (40)	0.913
Hypertension n (%)	243 (66)	238 (66)	245 (66)	257 (70)	255 (69)	0.211
Total cholesterol, mmol/l	5.12±1.22	5.53±1.11	5.82±1.19	5.92±1.34	6.23±1.22	<0.001
HDL cholesterol, mmol/l	1.24±0.36	1.16±0.34	1.11±0.31	1.03±0.28	0.98±0.28	<0.001
Non-HDL cholesterol, mmol/l	3.88±1.16	4.37±1.09	4.71±1.13	4.89±1.27	5.25±1.20	<0.001
Current smoker, n (%)	260 (71)	243 (68)	272 (74)	280 (76)	304 (82)	<0.001
Family history of CAD, n (%)	126 (34)	119 (33)	102 (28)	103 (28)	125 (34)	0.446
Prior MI, n (%)	147 (40)	175 (49)	170 (46)	185 (50)	204 (55)	<0.001
Prior stroke, n (%)	15 (4)	24 (7)	11 (3)	14 (4)	18 (5)	0.720
Atrial fibrillation, n (%)	49 (13)	47 (13)	43 (12)	38 (10)	54 (15)	0.985
On dialysis (%)	6 (1.6)	1 (0.2)	6 (1.6)	7 (1.9)	7 (1.9)	0.283
No of diseased vessels	2.17±0.84	2.27±0.83	2.24±0.85	2.32±0.78	2.28±0.82	0.128
LMT lesion, n (%)	34 (9)	21 (6)	41 (11)	29 (8)	24 (7)	0.437
Arterial bypass to LAD, n (%)	117 (32)	112 (31)	126 (34)	124 (34)	129 (35)	0.791
LVEF (%)	65.3±12.7	64.0±12.9	65.3±11.9	63.9±13.5	63.4±13.4	0.136
Revascularisation-isolated PCI, n (%)	139 (38)	117 (33)	96 (26)	98 (27)	85 (23)	<0.001
Medications, n (%)						
Aspirin	279 (76)	264 (74)	266 (72)	253 (68)	251 (68)	0.006
ACE inhibitors	20 (5)	16 (4)	16 (4)	24 (7)	14 (4)	0.729
β-blockers	88 (24)	84 (23)	113 (31)	123 (33)	111 (30)	0.003
Statins	84 (23)	60 (17)	60 (16)	67 (18)	57 (16)	0.035
Fibrates	3 (0.8)	8 (2.2)	10 (2.7)	5 (1.4)	7 (1.9)	0.551
Niacin	37 (10)	29 (8)	28 (8)	37 (10)	23 (6)	0.214

*p Value for trend for all comparisons across triglyceride quintiles.
BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LAD, left anterior descending; LMT, left main trunk; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

mortality even after adjustment for cholesterol levels and other covariates in secondary prevention of CAD. Second, the mortality risk of triglyceride was observed in patients with significant CAD who had achieved complete revascularisation. Finally, there were no interactions in each subgroup, although associations of fasting triglyceride level with cardiac mortality after complete revascularisation were obvious in men, patients with low HDL cholesterol levels and patients not receiving statins. Our findings therefore suggest that fasting triglyceride levels indicate mortality risk in the secondary prevention of CAD regardless of the presence or absence of other concomitant cardiovascular risks.

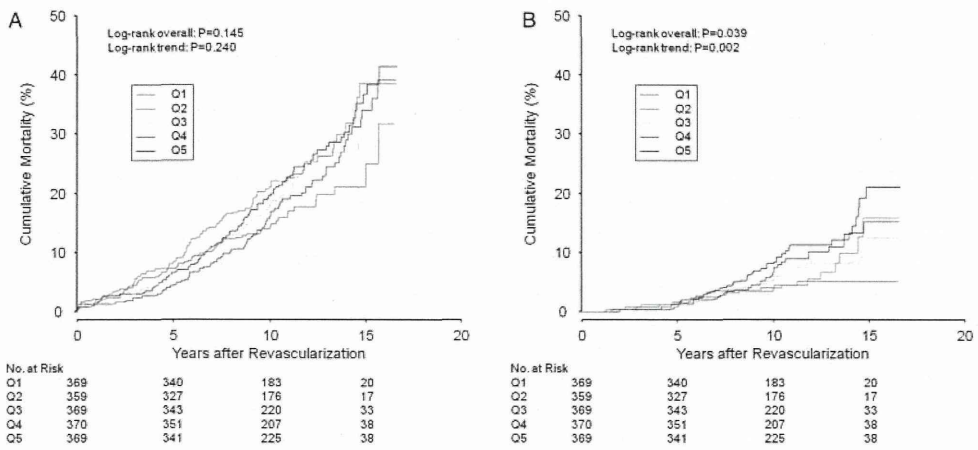

Figure 1 Cumulative mortality curves according to the quintiles of triglyceride levels for (A) all-cause deaths and (B) cardiac deaths. p Values for overall log-rank tests indicate whether there is a difference in the five different mortality curves (p=0.145 for all-cause death, p=0.039 for cardiac death). p Values for log-rank trend test indicate whether increased levels of triglycerides are associated with increased cumulative survival (p=0.240 for all-cause death, p=0.002 for cardiac death). This figure is only reproduced in colour in the online version.

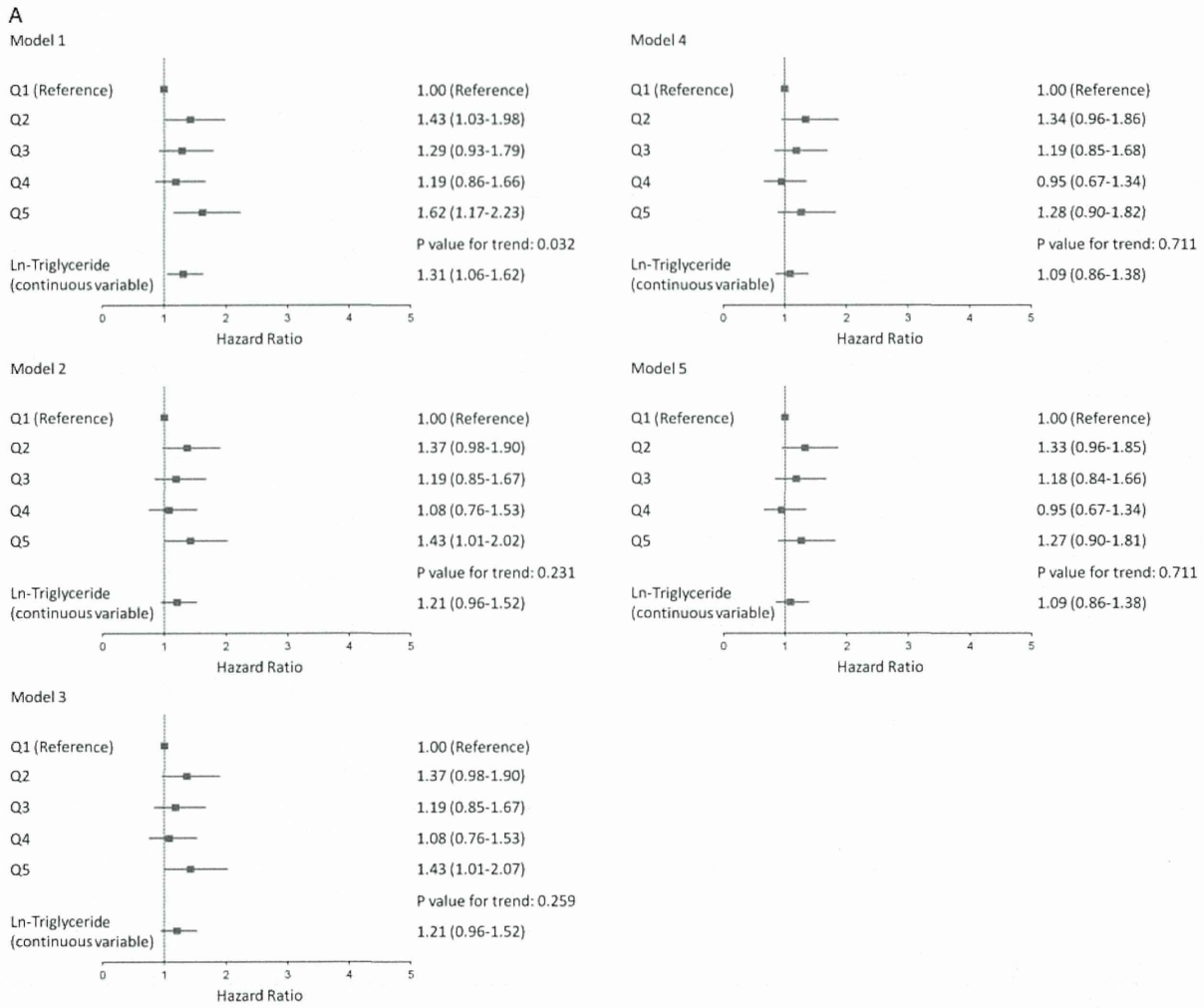

Figure 2 HR for mortality according to the quintiles of triglyceride levels: (A) all-cause deaths; (B) cardiac deaths. Model 1 adjusted for age and gender; Model 2 adjusted for age, gender, total and HDL cholesterols; Model 3 adjusted for age, gender, non-high-density lipoprotein (HDL) and HDL cholesterol; Model 4, adjusted for variables in model 2 plus hypertension, diabetes mellitus, prior myocardial infarction, prior stroke, atrial fibrillation, dialysis, left ventricular ejection fraction, number of diseased vessel, left main trunk lesion, isolated percutaneous coronary intervention, use of aspirin, use of angiotensin-converting enzyme (ACE) inhibitors, use of statins and use of niacin for all-cause death and the same variables other than hypertension, use of aspirin and use of ACE inhibitors for cardiac death; Model 5, adjusted for non-HDL cholesterol plus same variables in model 4 other than total cholesterol. Ln, natural logarithm-transformed. This figure is only reproduced in colour in the online version.

In the primary prevention of CAD the independent association of triglyceride levels with the morbidity and mortality rates of CAD has long been a controversial issue.[11–13] In previous case-control studies, triglyceride levels have been identified as one of the risk factors for CAD even after adjustment for total and HDL cholesterol levels.[14–17] Although most population-based cohort studies have shown a univariable association between triglyceride levels and CAD, the relationship becomes non-significant or weak after adjustment for total and/or HDL cholesterol levels.[13] There are at least four meta-analyses of population-based prospective studies regarding the relationships between triglyceride levels and morbidity and mortality rates of cardiovascular disease.[5–8] Of these, three have similar conclusions. Hokanson and colleagues reported the results of a meta-analysis of 46 413 men and 10 864 women from the USA and European countries.[5] In the univariable analysis the relative risk of triglyceride (per 1 mmol/l) for the composite of fatal and non-fatal cardiovascular disease was 1.32 in men and 1.76 in women. After adjustment for HDL cholesterol, these relative risks were attenuated to the modest levels of 1.14 in men and 1.37 in women. A recent updated meta-analysis that examined 262 525 subjects from the USA and European countries revealed a 1.7 times higher risk for the composite of fatal and non-fatal CAD at the upper triglyceride tertile compared with the lower triglyceride tertile in the adjusted analysis.[7] Another meta-analysis that examined 96 224 men and women from the Asian and Pacific populations showed that the risk for the composite of fatal and non-fatal CAD in individuals in the top triglyceride quintile was 1.8 times greater than those in the bottom triglyceride quintile after adjustment for several established risk factors.[6] In the most recent and robust evidence from the Emerging Risk Factors Collaboration, 302 430 people were examined in 68 prospective studies.[8] With adjustment for age and sex, triglycerides showed a strong stepwise association with fatal and non-fatal CAD. However, after adjustment for standard risk factors and other lipid measures such as non-HDL and HDL cholesterol levels, the association between triglycerides and CAD was no longer significant.[8] The American Heart Association has recently suggested that the independence of the triglyceride level as a causal factor in developing CAD remains debatable, but triglyceride levels appear to provide unique information and can be used as a biomarker of risk.[18]

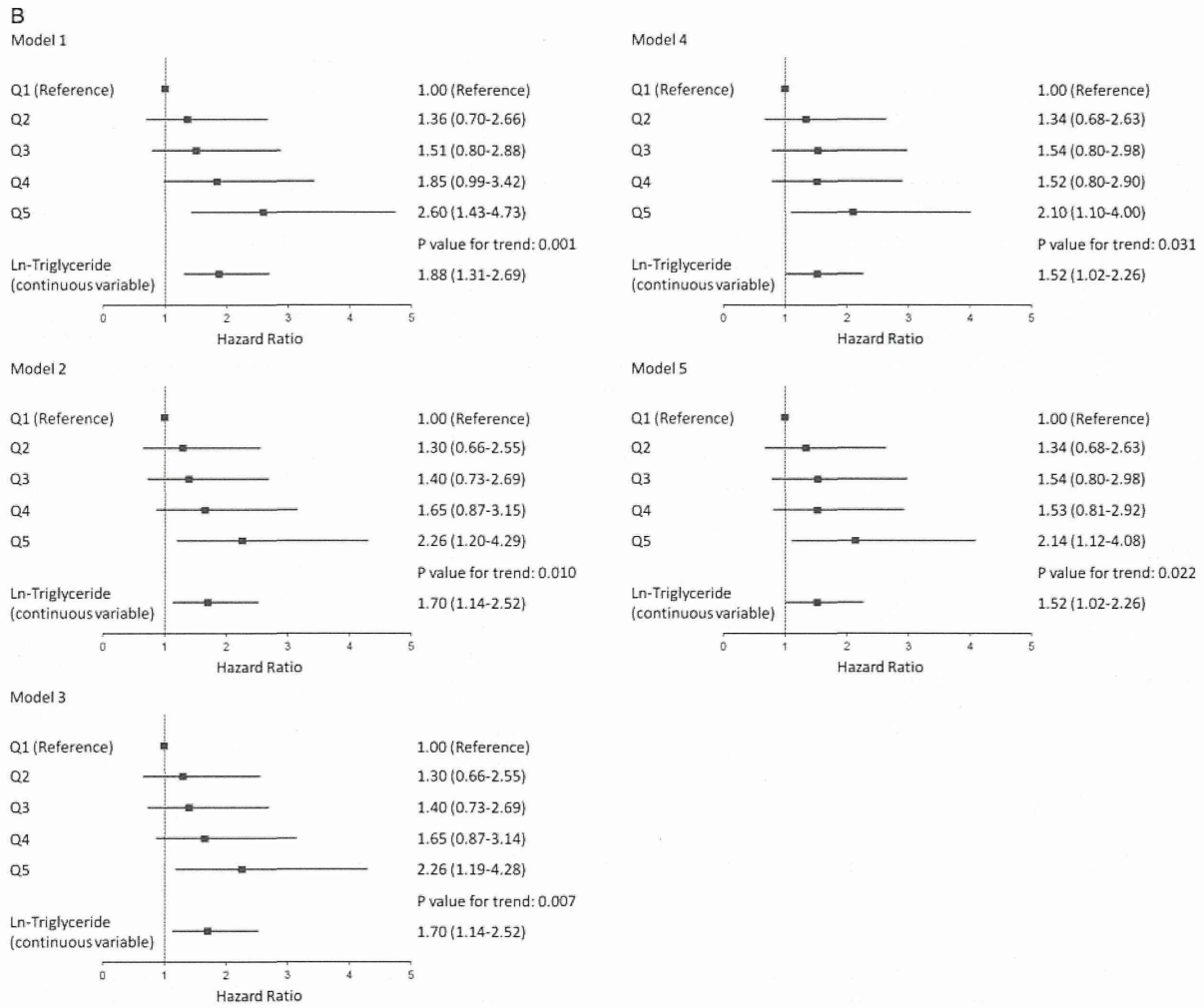

Figure 2 Continued.

Although individuals enrolled in some of the population-based prospective studies included in the abovementioned meta-analysis had a history of CAD, the percentage of such individuals was very low (<15%). Furthermore, there are no subdivided analyses regarding individuals with CAD. In the case of secondary prevention of CAD, only one report suggesting a significant relationship between triglyceride levels and long-term prognosis is available. von Eynatten and colleagues reported that, in patients with CAD, fasting triglyceride levels were associated with a high incidence of secondary cardiovascular events (ie, composite of cardiovascular death, non-fatal MI and stroke) during a median follow-up term of 57 months, even after adjustment for other lipid and adiponectin levels, with an HR of 1.5 which is identical to the results of our study (as a continuous variable).[19] However, the main purpose of their study was not to assess the relationship between triglyceride levels and prognosis but to investigate whether adiponectin is a useful prognostic predictor in patients with CAD and to compare the values of adiponectin for secondary risk stratification with the prognostic role of markers of dyslipidaemia (ie, triglyceride, low-density lipoprotein (LDL) and HDL cholesterol). Their patients were a mixture of those who had undergone non-invasive or invasive (PCI and CABG) treatment. Except for the severity of CAD, the details related to CAD and type of treatment were not specifically described and were not adjusted for in the multivariable analysis (eg, whether PCI was successful or whether complete revascularisation was performed were not mentioned and no adjustment was made for them). Our study shows that, in patients with complete revascularisation, fasting triglyceride levels were associated with increased cardiac mortality for a long-term follow-up period (>10 years). It was important to assess data only from patients who had achieved complete revascularisation because initial CAD events may be prevented or delayed by complete coronary revascularisation, even in patients with severe coronary atherosclerosis. This selection minimises the bias of treatment procedures for initial CAD events. Therefore, we specifically assessed the effect of fasting triglyceride levels on long-term mortality among the secondary prevention cohort of patients with CAD in this study.

We also assessed the possible interactions of triglyceride levels and cardiac mortality with age, gender, presence or absence of DM, total and HDL cholesterol and use of statins. There were no statistically significant interactions between the subgroups, which indicated that the relationship between triglyceride levels and high cardiac mortality was not affected by these factors. A strong relationship was found between triglyceride levels and cardiac mortality in men, patients with low HDL and patients not receiving statins. Although the Framingham Heart Study suggested that a high triglyceride level was a predictor of the incidence of cardiovascular disease in women,[20] the triglyceride level in our study did not show a significant relationship with increased cardiac mortality in women with CAD. In general,