ABSTRACT

BACKGROUND: The purpose of this study was to investigate the prognostic value of quadriceps isometric strength (QIS) in coronary artery disease (CAD).

METHODS: The study population consisted of 1314 patients aged >30 years (64.7 ± 10.6 years, 1051 male) with CAD who were hospitalized for acute coronary syndrome or coronary artery bypass grafting. Maximal QIS was evaluated as a marker of leg strength and expressed relative to body weight (% body weight). The primary and secondary endpoints were all-cause death and cardiovascular (CV) death, respectively.

RESULTS: During a mean follow-up of 5.0 ± 3.5 years, corresponding to 6537 person-years, there were 118 all-cause deaths and 63 CV deaths. A higher QIS remained associated with decreased all-cause mortality and CV mortality risks (hazard ratio for increasing 10% body weight of QIS 0.77, 95% confidence interval 0.67-0.89, \( P < .001 \) for all-cause death; hazard ratio 0.66, 95% confidence interval 0.54-0.82, \( P < .001 \) for CV death) after adjustment for other prognostic factors. The inclusion of QIS significantly increased both continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) for all-cause death (cNRI: 0.25, \( P = .009 \); IDI: 0.007, \( P = .030 \)) and CV death (cNRI: 0.34, \( P = .008 \); IDI: 0.013, \( P = .008 \)).

CONCLUSIONS: A high level of quadriceps strength was strongly associated with a lower risk of both all-cause and CV mortality in patients with CAD. Evaluation of QIS offered incremental prognostic information beyond pre-existing risk factors.

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KEYWORDS: Coronary artery disease; Muscle strength; Prognosis

Frailty in the elderly has become a high-priority theme in cardiovascular (CV) medicine.\(^1\) Skeletal muscle weakness is one of the phenotypes of frailty\(^4\) and is strongly associated with reduced exercise capacity\(^5,6\) and physical disability.\(^7\) Recent studies have indicated that skeletal muscle strength is a prognostic factor in community-dwelling individuals,\(^8\) chronic heart failure,\(^11,12\) and in different patient populations.\(^13\) We previously reported that quadriceps isometric strength (QIS), which can be measured accurately in a clinical setting, is a strong predictor of exercise capacity.
in patients with coronary artery disease (CAD). In addition, promoting physical activity is one of the main components of cardiac rehabilitation, and QIS is considered to be more clinically relevant to predicting physical activity and mobility disability than grip strength. However, it is not clear whether QIS can also be used to stratify prognosis in CAD patients.

The purpose of this study was to investigate the prognostic value of QIS in CAD.

**METHODS**

**Study Population**

A cohort of 1988 consecutive CAD patients admitted to Kitasato University Hospital from September 2000 to September 2012 for acute coronary syndrome, defined as acute ST-segment elevation, non-ST-segment elevation myocardial infarction, or unstable angina diagnosed according to American College of Cardiology/American Heart Association guidelines, or patients undergoing coronary artery bypass grafting were screened in the study. After excluding 335 patients with orthopedic and/or neurologic comorbidities limiting activities of daily living, 87 with missing baseline QIS measurements, 71 who died before QIS measurement, 49 with indication for thoracic or abdominal aortic aneurysm surgery, 30 unable to walk without assistance, and 102 with unstable medical conditions, 1314 patients were finally included in the study.

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Kitasato University Hospital.

**Maximal QIS Measurement**

Maximal QIS was measured with a hand-held dynamometer (μ Tas; ANIMA, Tokyo, Japan). Patients sat on a bench, and the dynamometer was fixed to a rigid bar. Five-second maximal isometric voluntary contractions of the quadriceps were collected 3 times successively for both legs in all patients, with the knee joint angle fixed at 90° of flexion and hip joint angle set at approximately 90° of flexion. The right and left quadriceps were tested consecutively, with a rest period of 30 seconds provided between sets of bilateral contractions. Electrocardiographic data were monitored continuously via telemetry. Patients were instructed not to hold their breath during contractions to avoid the Valsalva maneuver. The highest strength values on the right and left sides were averaged and expressed as absolute value (kg) and relative to body weight (% BW).

**Clinical Endpoint**

The primary and secondary endpoints of this study were all-cause death and CV death, respectively. Cardiovascular death was defined as death caused by any of the diseases classified in International Classification of Diseases, 10th Revision codes I00-I99. The length for both events was calculated as the number of days from the date of QIS measurement to the date of the event. The cause of death was judged independently by 2 physicians. If the decisions of the 2 physicians differed, they reached a consensus through discussion.

**Statistical Analysis**

Continuous variables are expressed as the means ± standard deviation. Categorical variables are expressed as numbers and percentages. We divided the cohort into 4 groups according to the quartiles of maximal QIS: quartile 1 (6.9%-35.0% BW), quartile 2 (35.1%-44.8% BW), quartile 3 (44.9%-55.9% BW), and quartile 4 (56.0%-112.0% BW). Baseline characteristics were compared by 1-way analysis of variance, Kruskal-Wallis test, or the χ² test where appropriate.

We used univariate and multivariate Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the endpoints. In multivariable analyses, all of the variables with univariate associations with outcome at P < .10 were included in the model. To evaluate the incremental prognostic predictive capability of QIS, we constructed a logistic model for both all-cause death and CV death using the variables that were shown to be independent predictors of outcome except QIS (RISKs model). We also constructed logistic models by adding QIS to that model (RISKs + QIS model), and predictive capabilities were compared with area under the curve (C statistics), continuous net reclassification improvement (cNRI), and integrated discrimination improvement (IDI). The cNRI and IDI have been developed as more sensitive statistical methods to quantify model improvement with the addition of a new variable to an existing clinical model. Briefly, NRI summarizes net changes in proportion of correctly upward classified events and downward classified nonevents with subtraction of the proportions of incorrectly downward classified events and upward classified nonevents when a novel predictor is added to a pre-existing model. The IDI is a measure of reclassification representing the average increase in model sensitivity assuming no decrease in model specificity. The cumulative probabilities of all-cause and CV death were visualized on a Kaplan-Meier curve using the log-rank test to compare cumulative events.

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**CLINICAL SIGNIFICANCE**

- A high level of quadriceps strength was strongly associated with lower risks of all-cause and cardiovascular mortality in patients with coronary artery disease.
- The evaluation of quadriceps strength provided incremental prognostic information beyond that provided by other independent risk predictors.
- Measurement of muscle strength could be widely used as a meaningful, noninvasive, and repeatedly measurable prognostic indicator in this population.
A 2-tailed \( P \) value < .05 was considered to indicate statistical significance. Analyses were performed using SPSS 22.0 (IBM, New York, NY), STATA version 13.0 (StataCorp, College Station, Tex), and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS
The mean age of the study population was 64.7 ± 10.6 years, and 80% of the patients were male. There were no cardiac events or ischemic ST-T changes during QIS measurements, and a total of 7884 quadriceps contractions were carried out by the study population.

Table 1 shows the baseline characteristics stratified by QIS quartiles. A decreased QIS was associated with older age, lower percentage of smoking, and a higher percentage of female patients, coronary artery bypass grafting, hypertension, diabetes, previous angina, previous heart failure, previous stroke and/or transient ischemic attack, end-stage renal disease, and multivessel CAD.

During a mean follow-up of 5.0 ± 3.5 years, corresponding to 6537 person-years, there were 118 all-cause deaths and 63 CV deaths. Table 2 shows the results of univariate and multivariate Cox regression analyses. Even after adjusting by other prognostic factors, QIS was still an independent predictor of both all-cause death (HR for a 10% BW increase of QIS 0.77; 95% CI, 0.67-0.89; \( P < .001 \)) and CV death (HR for a 10% BW increase of QIS 0.66; 95% CI, 0.54-0.82; \( P < .001 \)).

With regard to the predictive capability for all-cause mortality, the results of receiver operating characteristic analysis indicated that the area under the curve of the RISKs + QIS model (0.74; 95% CI, 0.69-0.79) was not significantly superior to that of the RISKs model (0.73; 95% CI, 0.68-0.78) (\( P = .26 \)). Similarly, the area under the curve for prediction of CV death was 0.78 (95% CI, 0.72-0.83) for the RISKs + QIS model and 0.74 (95% CI, 0.68-0.81) for the RISKs model (\( P = .07 \)). However, the inclusion of QIS in the RISKs model was associated with significant increases in both cNRI (0.25; \( P = .009 \)) and IDI (0.007; \( P = .030 \)) for all-cause death. Similarly, both cNRI (0.34; \( P = .008 \)) and IDI (0.013; \( P = .008 \)) were improved significantly when QIS was added to the RISKs model for CV death.

Figure 1 shows Kaplan-Meier curves regarding both outcomes for each QIS quartile. There was a significant difference in cumulative events for both all-cause and CV mortality. The cut-off values defining the quadriceps isometric strength quartiles were 35.0% BW, 35.1%-44.8% BW, 44.9%-55.9% BW, and 56.0% BW for quartile 1 to 4, respectively.

% BW = percentage of body weight; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.
death across QIS quartiles (log rank: \( P < .001 \) for both). In addition, inverse associations were observed between increasing quartiles of QIS and adjusted HR for both all-cause and CV death (Figure 2). Patients in QIS quartiles 3 and 4 had 60% and 62% lower risk of all-cause death compared with those in QIS quartile 1, and the same was true for CV death. The association of QIS with the primary and secondary endpoint was consistent across a number of key risk subgroups (Figure 3).

### DISCUSSION

The primary finding of the present study was that a high level of maximal QIS is strongly associated with lower risks of all-cause and CV mortality in patients with CAD. Each 10% BW increase of maximal QIS is associated with reductions of 23% and 34% in risks of all-cause and CV mortality, respectively, even after adjustment for several independent variables. This association was consistent across a variety of subgroups. Moreover, maximal QIS

### Table 2: Hazard Ratio for All-Cause and Cardiovascular Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-Cause Death</th>
<th>CV Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate Cox Regression</td>
<td>Multivariate Cox Regression</td>
</tr>
<tr>
<td></td>
<td>HR 95% CI P Value</td>
<td>HR 95% CI P Value</td>
</tr>
<tr>
<td>Age per 1 y</td>
<td>1.07 1.05-1.09 &lt;.001</td>
<td>1.04 1.02-1.07 &lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.93 0.60-1.43 .730</td>
<td>0.78 0.44-1.37 .379</td>
</tr>
<tr>
<td>Body mass index per 1 kg/m²</td>
<td>0.88 0.82-0.93 &lt;.001</td>
<td>0.91 0.85-0.97 .003</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.85 0.59-1.23 .390</td>
<td>0.42 0.24-0.72 .002</td>
</tr>
<tr>
<td>PCI</td>
<td>0.59 0.41-0.86 0.010</td>
<td>0.84 0.57-1.25 .397</td>
</tr>
<tr>
<td>CABG</td>
<td>1.37 0.94-2.01 0.100</td>
<td>1.80 1.09-2.98 .022</td>
</tr>
<tr>
<td>Medication</td>
<td>1.40 0.93-2.10 0.110</td>
<td>1.30 0.69-2.44 .423</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.11 0.76-1.61 0.600</td>
<td>1.37 0.81-2.33 0.245</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.33 0.92-1.90 0.130</td>
<td>1.41 0.86-2.31 .173</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.60 0.37-0.98 0.040</td>
<td>0.56 0.30-1.15 0.120</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.77 0.52-1.14 0.190</td>
<td>0.70 0.41-1.21 0.202</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.69 0.48-1.00 0.050</td>
<td>0.70 0.43-1.16 0.164</td>
</tr>
<tr>
<td>Previous angina</td>
<td>1.09 0.75-1.57 0.650</td>
<td>1.25 0.76-2.06 0.375</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1.19 0.80-1.77 0.400</td>
<td>1.69 1.01-2.83 0.045</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>3.03 1.98-4.63 0.001</td>
<td>2.06 1.31-3.24 0.002</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>3.15 2.04-4.88 0.001</td>
<td>2.22 1.41-3.49 0.001</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>2.79 1.29-6.06 0.010</td>
<td>1.69 0.76-3.78 0.202</td>
</tr>
<tr>
<td>LVEF per 5%</td>
<td>0.93 0.86-1.01 0.090</td>
<td>0.96 0.89-1.05 0.380</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.51 1.03-2.21 0.040</td>
<td>1.23 0.83-1.83 0.294</td>
</tr>
<tr>
<td>QIS per 10% BW</td>
<td>0.65 0.57-0.74 &lt;.001</td>
<td>0.77 0.67-0.89 &lt;.001</td>
</tr>
</tbody>
</table>

% BW = percentage of body weight; CABG = coronary artery bypass grafting; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; QIS = quadriceps isometric strength; TIA = transient ischemic attack.

**Figure 1** Kaplan-Meier curves for all-cause and cardiovascular (CV) death according to quartiles (Q) of maximal quadriceps isometric strength. The cut-off values defining the quadriceps isometric strength quartiles were ≤35.0% body weight (BW), 35.1%-44.8% BW, 44.9%-55.9% BW, and ≥56.0% BW for Q1 to Q4, respectively.
provided incremental prognostic information beyond the preexisting prognostic risk factors in CAD patients.

With regard to the relationship between frailty and prognosis, Heitmann et al\textsuperscript{21} reported that having smaller thighs was associated with the development of CV morbidity and early mortality even after adjustment for abdominal waist circumference, lifestyle, and CV risk factors. In addition, these authors reported that the outcomes were more closely related to thigh circumference than to waist circumference. In addition, Newman et al\textsuperscript{8} conducted a follow-up survey over approximately 5 years that measured muscle strength and muscle size, determined by either computed tomography area or dual energy X-ray absorption regional lean mass in 2292 men and women aged from 70 to 79 years. They reported that skeletal muscle strength was more useful for predicting mortality than skeletal muscle mass. Similar results have recently been reported in community-dwelling elderly people. These results suggest that muscle strength as a marker of muscle quality is more important than quantity in estimating mortality risk.

Two recent studies showed that muscular strength predicts all-cause or CV mortality in patients with CAD\textsuperscript{22,23}. However, these 2 studies had some limitations. First, only older adults were included in the study population, so the results could not be extrapolated to relatively young patients. Second, the sizes of the study populations (629 and 309, respectively, vs 1314 in the present study) and the numbers of events (78 and 28, respectively, vs 118 in the present study) were smaller, and the follow-up periods (2.9 years and 6 months, respectively, vs 5.0 years in the present study) were shorter than those of the present study. Finally, although muscle strength had been shown to be an independent predictor even after adjusting for other factors, no incremental prognostic power of muscle strength was demonstrated in either of these previous studies. To our knowledge, this is the first study to demonstrate the incremental prognostic value of skeletal muscle strength in a large cohort of CAD patients.

**Figure 2** All-cause and cardiovascular death risk across maximal quadriceps isometric strength quartiles (Q).

*Adjusted for age, body mass index, previous heart failure, and previous stroke and/or transient ischemic attack for all-cause death, and age, body mass index, coronary artery bypass grafting, previous heart failure, previous stroke and/or transient ischemic attack, end-stage renal disease, and coronary artery multivessel disease for cardiovascular (CV) death. % BW = percentage of body weight; CI = confidence interval; HR = hazard ratio; QIS = quadriceps isometric strength.
We used a hand-held dynamometer to measure QIS. In a clinical setting, functional muscular strength is traditionally evaluated on a 6-point grading scale with manual muscle testing. However, the reliability of this subjective manual muscle evaluation when testing larger muscle groups has been shown to be problematic. Isokinetic dynamometry provides accurate assessments of dynamic and static muscle strength and may be recommended for clinical studies. However, its utility in clinical practice is limited, because the equipment is costly and not portable. Hand-held dynamometry has been used widely already in clinical practice because of its simplicity, objectivity, and responsiveness compared with manual muscle testing and isokinetic dynamometry.

The potential mechanism underlying the association between quadriceps strength and mortality in CAD patients has not been determined. Skeletal muscle weakness promotes exercise intolerance and physical inactivity. Reduced physical activity itself has been shown to be an independent risk factor for CV disease, and frailty and CV disease are seen frequently in the same subjects. The pathobiologies of frailty and CV disease indeed share several common factors, particularly a consistent correlation with the inflammatory biomarkers interleukin-6 and C-reactive protein. It is worth underscoring that a strict relationship has been demonstrated between muscle strength and circulating inflammatory markers, not only in healthy young and elderly subjects but also in patients with chronic disease. These findings support our hypothesis regarding the impact of skeletal muscle strength on all-cause and CV mortality. Importantly, resistance training can enhance muscle strength, muscle mass, and functional capacity, as well as positively modulate the inflammatory status not only in animals but also in both healthy and patient populations. These findings provide a biological rationale for a possible favorable effect of resistance training on the prognosis of CAD patients, which, however, remains to be confirmed.

Limitations of the Study
The present study had some limitations. First, exercise capacity data were not available for all participants, so we were unable to examine whether muscular strength is associated with premature mortality independent of exercise capacity. However, we showed recently that QIS is linked strictly to whole-body exercise capacity in CAD patients, which would have made it redundant to include both maximal QIS and peak oxygen consumption or peak metabolic equivalents in the same predictive model. Second,
we measured maximal QIS only once; repeated measurements would have provided information about the prognostic power of maximal QIS changes over time. Third, there were some unmeasured factors associated with mortality of CAD patients, such as baseline medications and socioeconomic status. Fourth, because of the relatively small number of events, especially CV deaths (n = 63), there is a problem of model overfitting in the multivariate Cox model. Finally, our study population was predominantly male. However, the results of subgroup analyses indicate that the high quadriceps strength has a protective effect on all-cause and CV mortality also in females. Thus, our results seem to be applicable in the female population, but further research on this topic is needed.

CONCLUSIONS

This study showed that a high level of quadriceps strength was strongly associated with lower risks of all-cause and CV mortality in patients with CAD. In this population the evaluation of QIS provided incremental prognostic information beyond that provided by other independent risk factors. Our results support the use of maximal QIS evaluation to stratify prognosis of CAD patients. Further studies are needed to clarify the impact of resistance training-induced increases in maximal QIS on survival in this population.

References


