Usefulness of Handgrip Strength to Predict Mortality in Patients With Coronary Artery Disease

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Handgrip strength (HGS) is a validated and simple technique to estimate skeletal muscular strength. Whether HGS is a predictor of overall mortality in patients with established coronary artery disease (CAD) is not known, this question is therefore addressed in the present study. We prospectively investigated a cohort of 691 patients with angiographically proven CAD. HGS was measured at baseline, and all-cause death as well as cardiovascular events was recorded over a period of up to 12 years. During a follow-up time of 9.2 ± 3.1 years, 31.3% (n = 216) of the study participants died. Further, 27.8% (n = 192) suffered major cardiovascular events and 56.6% (n = 391) any cardiovascular event. Cox proportional hazard model analysis showed a reduced mortality risk with higher HGS univariately (hazard ratio [HR] for each 5 kg increase in HGS 0.87 [95% confidence interval 0.82 to 0.92]; p <0.001), after adjustment for age and gender (HR 0.86 [0.79 to 0.94]; p = 0.001), and after further adjustment for conventional cardiovascular risk factors (HR 0.86 [0.79 to 0.94]; p = 0.001). Similarly, high HGS was protective of major cardiovascular events as well as of total cardiovascular events (HRs in the fully adjusted model 0.86 [0.78 to 0.94]; p = 0.002 and 0.89 [0.83 to 0.96]; p = 0.002, respectively). From these data, we conclude that HGS is an independent predictor of overall survival and of cardiovascular events in patients with CAD. **(Am J Cardiol 2020;129:5–9)**

Cardiorespiratory fitness and muscular strength are protective against cardiovascular events and premature mortality.[1] A recent analysis of UK Biobank data even implies that the association of physical activity and cardiovascular outcome is more prominently moderated by muscle strength than by cardiorespiratory fitness.[2] Handgrip strength (HGS) is a validated and widely used tool to measure muscular strength. It is a simple, inexpensive and non-invasive technique that correlates well with overall muscle strength.[3] Furthermore, HGS is recommended as the diagnostic tool of choice for the evaluation of sarcopenia and frailty[4] and has been suggested as a possible non-invasive screening tool for cardiovascular risk stratification.[5] Reduced HGS is associated with premature mortality and cardiovascular morbidity in population-based cohorts[6–8] and in elderly people.[9] However, the association of HGS with overall mortality or major cardiovascular events in patients with coronary artery disease (CAD) has not yet been studied even though CAD is the most common cause of death in Europe and the United States.[10,11] Thus, the prognostic value of HGS in this population is of special interest. We therefore investigated whether HGS is a predictor of mortality in CAD patients in a prospective cohort study including patients with angiographically proven CAD.

Methods

The design of this prospective cohort study has been described in detail previously.[12] In brief, we consecutively recruited 1,048 Caucasian patients between 2005 and 2008 at the Academic Teaching Hospital Feldkirch, Feldkirch, Austria. These patients were referred to coronary angiography for the evaluation of established or suspected CAD. Subjects who had suffered myocardial infarctions or acute coronary syndromes in the 3 months before the baseline examination were not enrolled. For this study, we included patients with angiographically proven CAD (n = 851). From this dataset, 691 patients had valid HGS measurements and entered final analysis. The study was approved by the Ethics Committee of the Medical University of Innsbruck and conducted in line with the Declaration of Helsinki. All participants gave written informed consent.

Anthropometric measurements such as height, weight, waist, and hip circumference were measured at baseline and body mass index (BMI) was calculated. Information on conventional cardiovascular risk factors was obtained using standardized interviews. Blood pressure (BP) was recorded via the Riva-Rocci method in sitting position at the day of

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See page 8 for disclosure information.

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hospital admission. The 2013 ESC/ESH guidelines were used to determine hypertension.[13] The diagnosis of T2DM was made according to current guidelines of the American Diabetes Association.[14] The Metabolic Syndrome was diagnosed according to harmonized Consensus Criteria by the International Diabetes Federation criteria 2009.[15] CAD was defined as the presence of any lumen narrowing at coronary angiography, and the extent of CAD as the number of significant coronary artery stenoses with lumen narrowing ≥50%, as described previously.[16] HGS was measured using a dynamometer in sitting position with the elbow flexed at 90° at the dominant hand 3 times in a row. The maximal value of these 3 measurements was used for further calculations, as has been suggested previously.[6] Venous blood samples were collected after an overnight fast of 12 hours before angiography. Biochemical analyses were performed as described previously.[12]

The cohort was followed for a period of up to 12 years. We recorded all-cause death, cardiovascular death including coronary death, fatal myocardial infarction (MI), sudden cardiac death, mortality from congestive heart disease as a result of CAD as well as non-coronary vascular death. Furthermore, non-fatal events including non-fatal MI, non-fatal stroke and need for revascularization by either coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) or non-coronary revascularization were recorded. Apart from all-cause death, 2 secondary end points were applied. First, a combined end point consisting of cardiovascular death, non-fatal MI and non-fatal stroke was used indicating major cardiovascular events (MACE). Second, a combined end point consisting of cardiovascular death, non-fatal MI, non-fatal stroke and need for revascularization (coronary or non-coronary) was applied indicating total clinically relevant cardiovascular events.

For end point adjudication, a national survey (Statistik Austria, Vienna, Austria) as well as hospital records was used to obtain data on time and cause of death. To assess non-fatal events, surviving participants were questioned at our institution and via telephone calls with standardized interviews every 2 years and in addition their hospital records were reviewed. PCI, CABG and non-coronary revascularization were considered as end points unless they were planned as a consequence of the baseline examination. Potential end points were independently reviewed by 2 of the authors (C.H.S. and A.V.). Follow-up was blinded to HGS and laboratory as well as coronary angiography baseline data. We could achieve a follow-up rate of 98.1%.

All analyses were performed with IBM SPSS V25.0 for macOS. Baseline characteristics and survival curves were calculated according to quartiles of HGS. To test for differences at baseline, the chi-quadrat test for trend was used for categorical variables. For continuous variables, the Jonckheere-Terpstra test was applied. Analysis of covariance was used to check for significant predictors of HGS at baseline. Unadjusted as well as adjusted hazard ratios (HR) were derived from Cox proportional hazards models. For Cox models, the continuous dependent variable (HGS) was divided by 5 and HRs were calculated indicating the changes in HR is with a 5 kg change in HGS. After univariant analysis (model 1) adjustment was made for age and gender (model 2) as well as for other cardiovascular risk factors including BMI, T2DM, hypertension, history of smoking, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) (model 3). Statistical significance was defined as a p value of <0.05. Results are given as mean (±standard deviation) if not otherwise specified.

Results

In our cohort of 691 CAD patients, there was a preponderance of male gender (71.1%) and a high prevalence of T2DM (28.1%), hypertension (73.7%), metabolic syndrome (44.9%) and history of smoking (61.9%). Details on baseline data are given according to quartiles of HGS (Table 1). In analysis of covariance, significant predictors of higher HGS were younger

Table 1
Baseline characteristics according to quartiles of handgrip strength

	Q1	Q2	Q3	Q4	p trend
Handgrip strength (kg)	0-26	26-36	36-45	>45	
Age (years)	70.4 8.5	67.7 ± 8.9	65.5 ± 9.7	57.4 ± 9.4	**<0.001**
Women	85%	35%	3%	0%	**<0.001**
Height (cm)	159.4 ± 7.1	166.8 ± 6.7	171.0 ± 5.4	174.9 ± 6.1	**<0.001**
Weight (kg)	69.7 ± 13.5	75.5 ± 12.9	81.9 ± 12.5	86.2 ± 12.8	**<0.001**
BMI (kg/m)	27.4 ± 5.0	27.2 ± 4.5	27.6 ± 3.7	28.1 ± 3.5	**0.008**
Waist circumference (cm)	97 ± 13	98 ± 11	101 ± 11	101 ± 11	**<0.001**
Type 2 Diabetes	33.8%	30.0%	22.4%	25.7%	0.045
Metabolic Syndrome	53.8%	40.6%	37.2%	49.1%	0.398
Hypertension	77.5%	73.5%	75.6%	68.6%	0.103
Smoker	35.6%	65.5%	70.5%	74.3%	**<0.001**
Total cholesterol (mg/dl)	200 ± 45	194 ± 50	185 ± 42	196 ± 47	0.185
LDL-C (mg/dl)	130 ± 42	125 ± 44	119 ± 38	130 ± 43	0.725
HDL-C (mg/dl)	61 ± 15	57 ± 17	54 ± 14	50 ± 14	**<0.001**
Triglycerides (mg/dl)	126 ± 58	135 ± 99	133 ± 83	160 ± 96	**0.004**
Statin treatment	53.1%	57.0%	50.0%	51.4%	0.458
Extent of CAD	1.53 ± 1.74	1.71 ± 1.72	1.76 ± 1.66	1.53 ± 1.57	0.561

BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; Extent of CAD = number of coronary artery stenosis >50% on angiography.

Bold print indicates statistical significance.

age (F = 154.1, p <0.001) male gender (F = 136.7, p <0.001), higher body height (F = 63.8, p <0.001) and the presence of T2DM (F = 5.5, p = 0.020). HGS did not correlate significantly with the number of significant coronary artery stenoses (Spearman's correlation coefficient r = 0.024, p = 0.537).

During a mean follow-up time of 9.2 ± 3.1 years, 216 participants (31.3%) died. We recorded 71 deaths from cardiovascular causes (10.3%), 69 non-fatal MIs (10.0%), 52 non-fatal strokes (7.5%), 102 PCIs (14.4%), 33 CABGs (4.8%) and 64 non-coronary revascularizations (9.4%). A total of 165 patients (23.9%) suffered a first MACE, and 270 patients (39.1%) suffered a first cardiovascular event overall.

Figure 1 shows survival according to quartiles of HGS. Prognosis improved with increasing HGS (log rank test p <0.001). Cox proportional hazard models revealed a significantly reduced risk of overall mortality univariately (HR for each 5 kg increase in HGS 0.87 [95% CI 0.82 to 0.92]; p <0.001) and after adjustment for age and gender (HR 0.86 [0.79 to 0.94], p = 0.001). This finding remained consistent after further adjustment for conventional cardiovascular risk factors (BMI, T2DM, hypertension, history of smoking, total cholesterol, LDL-C and HDL-C), with a HR of 0.86 [0.79 to 0.94], p = 0.001.

Because HGS depends on age and gender, we analysed our data according to age and gender subgroups (Figure 2). Cox proportional hazard models showed similar results for HGS as a predictor of mortality for male and female patients both univariately (HR 0.76 [0.70 to 0.83]; p <0.001 and HR 0.60 [0.47 to 0.77]; p <0.001, respectively) and in the fully adjusted model (HR 0.88 [0.79 to 0.96]; p = 0.007 and HR 0.62 [0.47 to 0.83]; p = 0.001, respectively). HGS also significantly predicted overall mortality in the subgroup of patients >65 years and in patients <65 years, with HRs of 0.79 [0.72 to 0.87]; p <0.001 and 0.83 [0.70 to 0.99]; p = 0.037, respectively.

Finally, we analysed our data focusing on major cardiovascular events and total cardiovascular events. HGS significantly predicted MACE (HR 0.86 [0.78 to 0.94]; p = 0.002) as well as total cardiovascular events (HR 0.89 [0.83 to 0.96]; p = 0.002) in the fully adjusted model (Table 2).

Discussion

From our data we conclude that HGS is an independent predictor of all-cause mortality and of cardiovascular events in patients with established CAD. To our knowledge, this is the first study to demonstrate the association of HGS with prognosis in this clinically relevant patient group. The magnitude of the association between HGS and outcomes in our study were comparable to those found in population-based studies.[6–8] Importantly, we found consistent results after multi-variant adjustment and in subgroup analyses according to age and gender. Our findings strengthen the hypothesis that the association between poor muscular strength and premature mortality is not only consistent across age and race categories but can also be reproduced in different disease states. Similar associations of HGS with outcomes as in our investigation including CAD patients have been described in patients with T2DM[17] and CKD.[18]

The mechanisms behind the association of HGS with overall mortality and cardiovascular disease are not fully elucidated. A plausible explanation is that low HGS is a general marker of ageing.[19] Indeed, it has been shown to have better concordance with frailty markers than chronological age itself.[20] Moreover, HGS reflects overall muscular fitness and physical function[3] which are established protective factors against cardiovascular disease.[1] Also, it correlates inversely with components of the metabolic syndrome[21] and other cardiometabolic risk factors.[22] Others propose that there might be a causal relation between muscle function and cardiovascular disease, a notion supported by one[23] but not by another[24] Mendelian randomization study. Further, UK Biobank data revealed that low HGS was associated with cardiac hypertrophy and remodeling[25] and that HGS and gait speed, another proxy for muscular strength, is associated with a mortality benefit.[26] With increasing evidence for the importance of the skeletal muscle as an endocrine organ,[27] the role of myokines[28] as a link between muscle strength and cardiovascular disease is of particular interest for further studies.

Important strengths of our investigation include the prospective design, considerable sample size, long follow-up

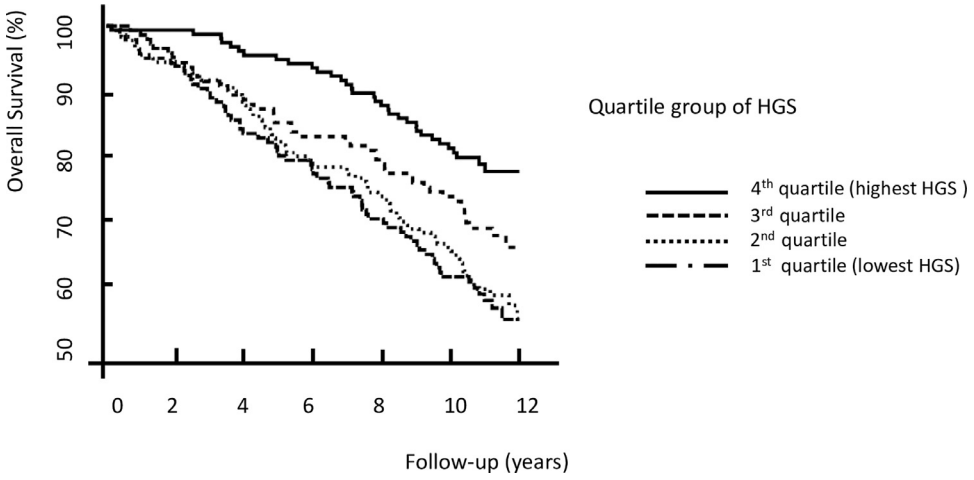

Figure 1. Overall survival according to quartiles of handgrip strength (HGS) in fourth quartile (highest HGS, solid line), third quartile (broken line), second quartile (dotted line), and first quartile (lowest HGS, semibroken line).

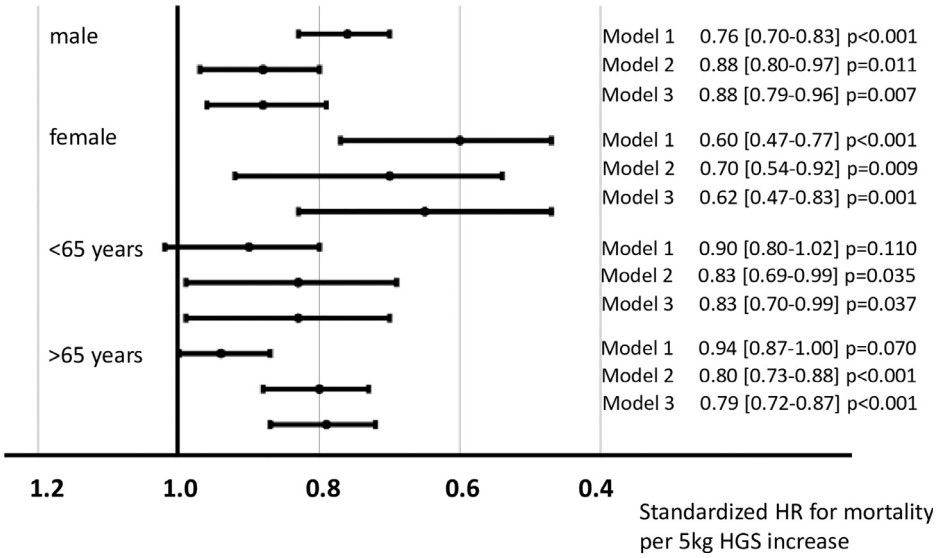

Figure 2. Handgrip strength (HGS) as predictor of mortality in subgroups according to age and gender. Model 1: univariant analysis; model 2: adjusted for age or gender; model 3: adjusted for age or gender, body mass index, type 2 diabetes mellitus, hypertension, smoking, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol; hazard ratios (HR) and (95% confidence intervals) are given per 5 kg increase in HGS.

Table 2
Handgrip strength as predictor of major cardiovascular events and total cardiovascular events

	Major cardiovascular events HR [95% CI]	Total cardiovascular events HR [95% CI]
Model 1	0.91 [0.85-0.97] p = 0.004	0.96 [0.91-1.01] p = 0.120
Model 2	0.86 [0.78-0.94] p = 0.002	0.80 [0.84-0.97] p = 0.004
Model 3	0.86 [0.78-0.94] p = 0.002	0.89 [0.83-0.96] p = 0.002

Model 1, univariate analysis; Model 2, adjusted for age and gender; Model 3, adjusted for age, gender, body mass index, type 2 diabetes mellitus, hypertension, smoking, total cholesterol, low density lipoprotein cholesterol and high density lipoprotein cholesterol; Hazard ratios (HR) and [95% confidence intervals] are given per 5 kg increase in handgrip strength.

time and high follow-up rate. Furthermore, our cohort was thoroughly characterized at baseline including coronary angiography. This allowed us to investigate a specific yet clinically important patient group. A limitation of our investigation is that no echocardiographic data were available; therefore, parameters of cardiac function such as left ventricular ejection fraction or hypertrophy could not be included in the analysis. Further, HGS measurement and interpretation has certain limitations. Although it is one of the most valid parameters of muscular strength, its measurement has not been standardized yet and is dependent on patient motivation.[29] In contrast to other vital signs or laboratory parameters, there are no universally agreed reference ranges for normal or abnormal HGS[30] although efforts to establish such have been made recently.[5,9]

In conclusion, we could demonstrate for the first time that HGS is an independent predictor of premature mortality, major cardiovascular events and total cardiovascular events in patients with CAD. In the light of this finding, further research addressing the link between skeletal strength and cardiovascular disease is warranted.

Author Contributions

BL: formal analysis, drafting of the manuscript, **DZ:** investigation, formal analysis, revision of the manuscript for intellectually important content, **AV**: investigation, formal analysis, revision of the manuscript for intellectually important content, **CFH:** investigation, formal analysis, revision of the manuscript for intellectually important content, **AM:** formal analysis, revision of the manuscript for intellectually important content, **SS:** formal analysis, revision of the manuscript for intellectually important content, **HD:** conceptualization, methodology, funding acquisition, investigation, drafting of the manuscript, **CHS:** conceptualization, methodology, investigation, formal analysis, drafting of the manuscript

Disclosures

The authors declare that they have no conflicts of interests.

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