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http://dx.doi.org/10.1016/j.ijcard.2014.04.015

Association of handgrip strength to cardiovascular mortality in pre-diabetic and diabetic patients: A subanalysis of the ORIGIN trial ☆

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ARTICLE INFO

Article history:
Received 25 March 2014
Accepted 2 April 2014
Available online 13 April 2014

Keywords:
Handgrip
Muscle strength
CVD risk
Type 2 diabetes
Dysglycemia

Type 2 diabetes (DM2) and lesser degrees of dysglycemia currently affect approximately 600 million people worldwide. These individuals are at high risk for future cardiovascular (CV) events and the presence of other well-established CV risk factors further increases their risk [1]. Muscle strength has been identified as an index of future CV risk and mortality [2–5]. Studies of the relationship between strength and CV outcomes have mainly been done in non-Hispanic Caucasians from high-income countries [6] and little data are available regarding this relationship in a wider, more heterogeneous sample of people with dysglycemia. We report the relationship between handgrip strength and CV events, and all-cause mortality based on a subanalysis of the ORIGIN (Outcomes Reduction with an Initial Glargine Intervention) clinical trial, the design and results of which have been previously published [7,8]. The ORIGIN trial recruited 12,537 people from 40 countries aged 50 and older with impaired fasting glucose/impaired glucose tolerance (12%) or DM2 (88%), who were either taking no glucose lowering agents or only 1 oral glucose lowering agent.

Three measurements of handgrip strength (HGS) were taken at baseline in 12,516 people (99.83% of total sample) using a Jamar Dynamometer (Sammons Preston Inc., Bolingbrook, IL) and mean HGS (kg) was calculated. The primary composite CV outcome of nonfatal myocardial infarction, stroke or CV death, and the individual components of this outcome, all-cause mortality, cardiac, carotid or peripheral revascularization and hospitalisation for heart failure were analysed. All HGS analyses (SAS software, version 9.1 for Solaris) were done using age adjusted handgrip strength (HGSA) for men and for women. The relationship between baseline characteristics and fifths of HGSA divided by quintiles was assessed using linear regression. The relationship between baseline HGSA and subsequent outcomes was assessed using Cox regression models before and after adjustment for body mass index (BMI), and waist (WC) and hip (HC) circumferences. Interactions of HGSA with gender were assessed by including an interaction term of gender and grip strength. Interactions of HGSA with region (South America, North America, Western Europe, Eastern Europe, Asia, India and Australia) were similarly assessed by including an interaction term of region and grip strength overall and by gender. Event curves for each fifth of HGSA for the primary composite and log-rank tests were used to compare each fifth to the highest fifth. The nominal level of significance for all analyses was $p < 0.05$.

12,516 individuals (35% women) of mean (SD) age 63.6 (7.8) years had a baseline HGS and were followed for a median of 6.2 years. As there was an interaction between gender and HGS with respect to prior CV disease ($p = 0.001$), all analyses were done separately for men and women (Tables 1A, 1B). In both men and women, higher fifths of HGSA were associated with a progressively lower prevalence of previous CVD ($p < 0.001$), positively related to weight, BMI and WC ($p < 0.001$) and inversely related to age, systolic blood pressure and creatinine ($p < 0.001$). There was an interaction between gender and HGS for all of the incident outcomes except stroke ($p < 0.006$). Therefore, results are presented separately for men and women. As both unadjusted and adjusted Cox regression analyses yielded similar results, only the adjusted data are presented (Fig. 1). The relationship between baseline HGSA divided into fifths and the incidence of the composite outcome is shown in Fig. 2. A nominal interaction ($p = 0.03$) was noted for HGSA to cardiovascular death by region for men but no other significant region interactions of the relationship of HGSA to outcomes were noted.

☆ The ORIGIN trial was funded by Sanofi. ORIGIN trial ClinicalTrials.gov Number: NCT00069784.
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Table 1A
Baseline characteristics in relation to fifths of age adjusted handgrip strength in men.

	Overall	1st (≤35.66)	2nd (35.67–37.73)	3rd (37.74–39.54)	4th (39.55–41.40)	5th (>41.4)	P value (trend)
n	8135	1627	1627	1627	1624	1630	
HGSA (kg)	38.47	33.96	36.75	38.62	40.48	42.52	<0.001
	(3.06)	(1.32)	(0.59)	(0.53)	(0.54)	(0.71)	
Weight (kg)	86.68	81.38	85.18	87.18	88.94	90.73	<0.001
	(16.12)	(12.91)	(14.62)	(16.47)	(16.69)	(17.82)	
BMI (kg/m^2)	29.33	28.14	28.94	29.48	29.80	30.30	<0.001
	(4.67)	(3.97)	(417)	(4.86)	(4.82)	(5.13)	
WC (cm)	101.61	99.96	100.92	102.09	102.20	102.90	<0.001
	(13.02)	(12.11)	(12.65)	(13.45)	(12.82)	(13.79)	
WHR	0.98	0.98	0.98	0.99	0.99	0.99	0.005
	(0.09)	(0.10)	(0.09)	(0.09)	(0.09)	(0.08)	
Previous CVD no.(%)	5507	1162	1116	1125	1077	1027	<0.001
	(67.70%)	(71.42%)	(68.59%)	(69.15%)	(66.32%)	(63.01%)	
SBP (mm Hg)	147.98	151.93	150.98	147.53	145.59	143.87	<0.001
	(22.80)	(23.56)	(23.39)	(21.86)	(22.34)	(21.77)	
Creatinine (μmol/L)	94.74	101.56	96.64	94.23	92.11	8916	<0.001
	(21.05)	(23.09)	(21.06)	(20.53)	(18.80)	(19.41)	

Data are mean (SD) or n (%). p value for trend was determined by linear regression. HGSA = age adjusted handgrip strength. BMI = body mass index. WC = waist circumference. WHR = waist to hip ratio. CVD = cardiovascular disease. SBP = systolic blood pressure.

This present analysis shows that greater handgrip strength is associated with a significantly lower incidence of death and both fatal and nonfatal cardiovascular events. This relationship was independent of adiposity, evident in both men and women and consistent across low, middle and high income countries. This extends previous findings in healthy adults [3–5] and in those with heart failure [9] or hypertension [10], to people with dysglycemia.

The few prior studies in mixed sex samples indicated that strength is more predictive of mortality in men [6]. It is notable therefore that we found a significantly stronger relationship between HGSA and incident outcomes in women. It is possible that a protective effect of HGS in men was obscured by other risk factors that increased their CV risk compared to women. The higher incidence of the primary composite in men than in women, 3.2/100 and 2.3/100 person-years respectively, illustrates this higher risk.

There are a variety of possible explanations which may account for the relationship between HGS and cardiovascular outcomes. Firstly, individuals with lower HGS may be less healthy overall than those with higher grip strength [11]. This possibility is supported by our finding of an inverse relationship between fifths of HGSA at baseline and baseline systolic blood pressure, creatinine and history of cardiovascular events. Secondly, strength is associated with participation in resistance training [3], associated with a lower CVD risk score [12] and lower risk of fatal and non-fatal CVD events [13]. HGS is also associated with both leisure time physical activity [14] and cardiorespiratory fitness (CRF) [3], previously shown to be protective against CVD mortality in people with DM2 [15,16]. While we did not assess CRF, previous studies show that adjusting for CRF attenuates, but does not eliminate, the association between strength and mortality [3,6,10]. Finally, strength may provide a direct protective effect against CV

Table 1B
Baseline characteristics in relation to fifths of age adjusted handgrip strength in women.

	Overall	1st (≤21.23)	2nd (21.24–22.30)	3rd (22.31–23.34)	4th (23.35–24.44)	5th (>24.44)	p value (trend)
n	4381	875	877	876	876	877	
HGSA (kg)	22.77	20.21	21.79	22.82	23.90	25.11	<0.001
	(1.75)	(0.84)	(0.30)	(0.30)	(0.31)	(0.41)	
Weight (kg)	76.83	71.65	74.95	77.44	78.87	81.22	<0.001
	(16.82)	(13.95)	(14.84)	(16.88)	(18.22)	(18.18)	
BMI (kg/m^2)	30.74	29.31	30.25	30.86	31.31	31.95	<0.001
	(6.09)	(5.23)	(5.56)	(6.05)	(6.45)	(6.69)	
WC (cm)	96.83	95.03	96.46	96.95	97.45	98.27	<0.001
	(14.05)	(13.81)	(13.49)	(13.87)	(14.16)	(14.72)	
WHR	0.90	0.90	0.90	0.90	0.90	0.90	0.953
	(0.09)	(0.10)	(0.09)	(0.09)	(0.09)	(0.09)	
Previous CVD no.(%)	1856	453	409	368	333	293	<0.001
	(42.36%)	(51.77%)	(46.64%)	(42.01%)	(38.01%)	(33.41%)	
SBP (mm Hg)	147.98	151.93	150.98	147.53	145.59	143.87	<0.001
	(22.80)	(23.56)	(23.39)	(21.86)	(22.34)	(21.77)	
Creatinine (μmol/L)	78.37	84.45	81.52	77.17	75.22	73.50	<0.001
	(19.76)	(21.90)	(20.42)	(18.65)	(17.94)	(17.51)	

Data are mean (SD) or n (%). p value for trend was determined by linear regression. HGSA = age adjusted handgrip strength. BMI = body mass index. WC = waist circumference. WHR = waist to hip ratio. CVD = cardiovascular disease. SBP = systolic blood pressure.