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Grip Strength Predicts Cardiac Adverse Events in Patients with Cardiac Disorders: An Individual Patient Pooled Meta-Analysis

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KEYWORDS

Grip strength, cardiac death, all cause death, heart failure, myocardial infarction

ABSTRACT

Objective: Grip strength is a well-characterized measure of weakness and of poor muscle performance, but there is a lack of consensus on its prognostic implications in terms of cardiac adverse events in patients with cardiac disorders.

Methods: Articles were searched in PUBMED, the Cochrane Library, BioMed Central and EMBASE. Main inclusion criteria were: patients with cardiac disorders (ischemic heart disease [IHD], heart failure [HF], cardiomyopathies, valvulopathies, arrhythmias); evaluation of grip strength by handheld dynamometer; relation between grip strength and outcomes. Endpoints of the study were cardiac death, all-cause mortality, hospital admission for HF, cerebrovascular accident (CVA) and myocardial infarction (MI). Data of interest were retrieved from the articles and after contact with authors and then pooled in an individual patient meta-analysis. Univariate and multivariate logistic regression was performed to define predictors of outcomes.

Results: Overall, 23480 patients were included from 7 studies. Mean age was 62.3 ± 6.9 years and 70% were male. The mean follow-up was of 2.82 ± 1.7 years. After multivariate analysis grip strength [difference of 5 Kg, 5xKg] emerged as an independent predictor of cardiac death (OR 0.84; 95%CI 0.79-0.89; $p<0.0001$), all-cause death (OR 0.87, 95%CI 0.85-0.89; $p<0.0001$) and of hospital admission for HF (OR 0.88, 95%CI 0.84-0.92; $p<0.0001$). On the contrary, we did not find any relationship between grip strength and occurrence of MI or CVA.

Conclusions: In patients with cardiac disorders, grip strength predicted cardiac death, all-cause death and hospital admission for HF.

Meta-analysis registration: The protocol of this meta-analysis is registered in PROSPERO (CRD42015025280).

KEY QUESTIONS

What is already known about this subject?

- There is a great interest in the assessment of frailty and/or physical performance in cardiac patients.
- Grip strength is an indicator of overall muscle function.
- The measurement of grip strength is simple, fast, cost-effective and can be performed also in bedridden patients.

What does this study add?

- Every 5 kg decrease of grip strength emerged as an independent predictor for cardiac death, hospital admission for heart failure and all-cause death in patients with cardiac disorders.

How might this impact on clinical practice?

- The systematic application of grip strength in the evaluation and management of cardiac patients might help physicians in the clinical decision-making process.

INTRODUCTION

In recent years, the mean age of cardiac patients has progressively increased. Accordingly, the issue of frailty is becoming pivotal for cardiologists. Frailty significantly affects clinical outcomes (including all-cause mortality), quality of life and the economic burden associated with healthcare [1-3]. In daily clinical practice, frailty can be assessed with several tests. Sarcopenia and low muscle strength are key elements of the frailty syndrome. Thus, it is not surprising that grip strength, an excellent indicator of overall muscle function [4], is part of many frailty diagnostic algorithms. Its predictive role in the general population on all-cause mortality has been already tested [5], showing that higher grip strength is associated with lower mortality. Previous studies have shown that grip strength strictly depends on age, sex, body size, muscle mass, socioeconomic status and level of physical activity [6-7]. It may be negatively influenced by chronic disease and nutritional status [6]. The large majority of previous studies on grip strength were not focused on cardiac patients [8-14]. Reliable data about the predictive role of grip strength in a cardiac population on cardiac endpoints (cardiac death, myocardial infarction, hospital admissions for heart failure) is not available. Thus, the aim of this individual patient pooled meta-analysis is to investigate the prognostic value of grip strength, especially for cardiac mortality, in patients with cardiac disease.

METHODS

We developed a systematic review and individual patient pooled meta-analysis following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement [15-16]. The protocol for this study was previously published on an international prospective register for systematic reviews (PROSPERO) with the number: CRD42015025280.

Search strategy

The search strategy was elaborated by RP in August 2016. The terms searched were ((grip strength) OR (handgrip)) AND ((cardiac death) OR ((cardiac) AND ((death) OR (mortality)))) OR (myocardial infarction) OR (acute coronary syndrome) OR (ST elevation myocardial infarction) OR (STEMI) OR (heart failure) OR (revascularization) OR (percutaneous coronary intervention) OR (PCI) OR (cardiac disease) OR (coronary artery disease)). The databases analyzed were from PUBMED, Biomed Central, Cochrane library and EMBASE. Only papers published in English and in peer-reviewed journals were selected. Two independent reviewers (GB, ET) analyzed the records and decided which deserved full-text analysis. In case of disagreement between the reviewers a third independent reviewer (MS) was involved to discuss the disagreement and take the final decision.

Selection criteria

The inclusion criteria for the studies were: i) observational or clinical trials with a relation between grip strength and cardiac outcome, ii) evaluation of grip strength by handheld dynamometer. The above-mentioned search strategy was designed to address these two main criteria. Nevertheless, our aim was to focus the attention on patients with cardiac disorders.

Then, we defined ischemic heart disease (IHD), heart failure (HF), cardiomyopathies, valvulopathies, arrhythmias as cardiac diseases of interest. Independent reviewers (GB, ET) analyzed all items generated by the search strategy and selected only those satisfying the third inclusion criteria: iii) study population affected by major cardiac disease. We included only data from patients showing one of these diseases at the time of the inclusion in the original study. Exclusion criteria were: i) duplicate reports; ii) duplicate of the sample population; iii) case reports/series iv); reviews or meta-analyses; v) lack of outcome of interest; vi) population without major cardiac disease; vii) cross-sectional studies. The same reviewers (GB, ET) independently analyzed the references of all the evaluated articles to avoid the eventual exclusion of additional studies. All the authors agreed on the final number of studies included.

Data abstraction, contact with authors, endpoints

The reviewers (GB, ET, MS) completed a database with data regarding: the journal, year of publication, hospital center, population characteristics, grip strength value, outcomes of interest. After selection of papers, corresponding authors were contacted and invited to share individual patient data. The following variables were asked: age, sex, anthropometric measurements (weight, height, body mass index [BMI]), cardiac risk factors (smoking habit, hypertension, diabetes, dyslipidemia), cardiac disease at the time of the inclusion in the study (IHD, HF, cardiomyopathies, valvulopathies, arrhythmias), comorbidities (chronic obstructive pulmonary disease [COPD], peripheral artery disease (PAD), chronic kidney disease [CKD], cerebrovascular accident [CVA]), grip strength expressed in Kg and outcomes of interest. The primary outcome of the study was cardiac death. Secondary outcomes were all-cause mortality, hospital admission for HF, myocardial infarction (MI) and CVA. Data obtained from each study were firstly checked against reported results and

queries were resolved with the corresponding authors. Data were assessed in a consistent manner across all studies with standard definitions and parameters.

Internal validity and quality appraisal

Two unblinded reviewers (RP, MS) independently evaluated the quality of the included studies using a modified version of the Newcastle-Ottawa Scale (NOS) for cohort studies [17] (Table 1s). Because of the design of the studies considered, the section “Comparability” and question 2 of the section “Selection” (“selection of the non-exposed cohort”) have not been considered [18]. Discrepancies between reviewers have been solved by consensus. No study was excluded on the basis of this analysis. The maximum score obtained was 6 and the minimum 5 (Table 1s).

Data analysis and synthesis

Demographics and other baseline characteristics were summarized in terms of mean \pm standard deviation (SD) for continuous variables (normal distribution assessed by Kolmogorov-Smirnov test). Categorical variables were expressed as absolute (number of participants) and relative frequencies (percentage). Variables were compared using the t-test for independent groups and the Chi-squared test as appropriate. Among the required variables, the following were available and considered in the present analysis: age, sex, weight, height, BMI, smoking habit, hypertension, IHD, COPD, CVA, grip strength. Additional information is detailed in Table 2s. To overcome potential limitation due to reproducibility of the test, grip strength was analysed as a 5 kg difference (5xKg). Univariate logistic regression was performed to evaluate the relationship between variables and outcomes (Table 3s). All the variables with a p value ≤ 0.05 at univariate analysis were entered into the multivariate model for assessing independent predictors of outcomes. To

establish the ability of grip strength to discriminate the primary outcome, receiver operating characteristics (ROC) curve with area under the curve (AUC) was also calculated. As suggested by recent consensus document, we stratified the analysis according to sex (male vs. female) [19] and age of the population (<65 years old vs. ≥ 65 years old). Using Youden's index (J), the best cut-off (c) point for grip strength was obtained, by the formula $J = \max_c \{ \text{Sensitivity}(c) + \text{Specificity}(c) - 1 \}$ [20]. The OR for the relationship between grip strength and cardiac death, all-cause death and hospital admission for heart failure was calculated for each single study and then pooled using the Mantel Haenszel method, with a random-effects method, and the generic inverse variance approach [21]. The weight of the individual studies was measured as the inverse of the estimated variance of the log odds ratio [21-22]. Heterogeneity across the trials has been assessed using the I^2 statistics, with a value of 0-24.9% considered insignificant, 25-49.9% mild, 50-74.9% moderate and $\geq 75\%$ considered severe [23]. Publication bias was appraised by Begg and Mazumdar rank correlation [23]. A p value <0.05 was considered statistically significant. Prometa software 3 (Internovi, Cesena, Italy), RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and SPSS version 21 (IBM, Italy) were the software used for statistical analyses.

RESULTS

Search strategy

A total of 2998 records were analyzed. After a first evaluation, 63 records were screened and of these 35 were excluded for different reasons (Figure 1). Twenty-eight full-texts were assessed for eligibility, but 1 was excluded because it was a duplicate, 2 had no data on outcomes, 4 were not focused on patients with major cardiac disease, 1 was a comment on another study. Therefore, 20 corresponding authors were contacted (Table 4s). Seven (35%) Authors agreed to share data [8-14] and the study populations of their studies were included in the individual patient pooled meta-analysis [8-14] (Figure 1, Table 1).

Population characteristics

Overall, the final study population included 23480 patients (Table 2). Mean age was 62.3 ± 6.9 years and 70% were male. At the inclusion in the study, 49.5% patients were affected by IHD. A detailed description of anthropometric measurements, risk factors and comorbidities is reported in Table 2.

Primary outcome

After a mean follow-up of 2.82 ± 1.7 years, cardiac death occurred in 523 (2.2%) patients. As expected, age and comorbidities significantly differed between patients who died or not for cardiac cause (Table 2). IHD was more frequent in patients with CD (3% vs. 2%, $p < 0.001$). Mean grip strength of patients who experienced CD was 27 ± 12 kg vs. 31 ± 11 kg in those survived ($p < 0.0001$). After multivariable analysis, grip strength (as 5xKg) emerged as independent predictor of cardiac death (OR 0.84; 95% CI 0.79-0.89; $p < 0.0001$), together with age (OR 1.10; 95% CI 1.08-1.12; $p < 0.0001$), male sex (OR 2.19; 95% CI 1.58-3.04;

p<0.0001), ischemic heart disease (OR 2.01; 95%CI 1.61-2.51; p<0.0001), hypertension (OR 3.01; 95%CI 2.10-4.32; p<0.0001), COPD (OR 1.46; 95%CI 1.05-2.05; p=0.025) and previous CVA (OR 7.4; 95%CI 5.62-9.79; p<0.0001). ROC curve analysis confirmed the ability of grip strength to discriminate cardiac death. The AUCs were: 0.61 (95%CI 0.56-0.66, p<0.001) for male <65 years old, 0.63 (95%CI 0.53-0.73, p=0.025) for female <65 years old, 0.65 (95%CI 0.61-0.69, p<0.001) for male ≥65 years old and finally 0.74 (95%CI 0.64-0.74, p<0.0001) for female ≥65 years old (Figure 1s-4s, table 5s). In the same four subgroups, the best cut-offs were 39, 24, 31 and 19 Kg, respectively (Figure 1s-4s, table 5s).

Secondary outcomes

The secondary outcomes all-cause mortality, hospital admission for HF, MI and cerebrovascular accident occurred in 2206 (9.4%), 884 (3.7%), 1010 (4.3%) and 63 (0.3%) patients, respectively. As reported in Table 3, grip strength (as 5xKg) emerged as an independent predictor of all-cause mortality (OR 0.87, 95%CI 0.85-0.89; p<0.0001) and of hospital admission for HF (OR 0.87, 95%CI 0.84-0.92; p<0.0001) (Table 3). On the contrary, we did not find any relationship between grip strength and occurrence of MI or CVA (Table 3).

Study-level meta-analysis

The analysis on aggregate data confirmed grip strength (for 5xKg change) as a predictor of cardiac death (OR 0.83, 95% CI 0.74-0.94, I^2 49%) (Figure 2). Similarly, grip strength was significantly associated with all-cause death and with the occurrence of hospital admission for HF (OR 0.86, 95% CI 0.81-0.91, I^2 18%; and OR 0.89, 95% CI 0.82-0.96, I^2 19%; respectively) (Figures 3-4). Of note the heterogeneity, expressed as I^2 degree, for cardiac death was mild and it was insignificant for all-cause death and hospital admission for HF.

The analysis showed the absence of publication bias (*Z value for Kendall's tau* -0.94; -0.75; -0.68 with *p* 0.35; 0.45; 0.50 for cardiac death, all-cause death and hospital admission for heart failure, respectively).

DISCUSSION

The main finding of this individual patient pooled meta-analysis is that grip strength is predictive of cardiac death and of hospital admission for heart failure in a population of patients with cardiac disease (mainly ischemic heart disease or heart failure).

In agreement with previous study [7], grip strength was also predictive of all-cause death.

A recent consensus document suggested grip strength as a tool to discriminate clinically relevant weakness [19]. The clinical implication of relevant weakness is of paramount importance because it is associated with a significant increase in mortality. The consensus document suggested different cut-offs according sex (male vs. female). Our findings confirmed the main results of the consensus document. After stratification of the study population according to sex (male vs. female) and age (<65 vs. ≥65 years), we identified best cut-offs consistent with those suggested for the identification of clinically relevant weakness [19]. Our ROC curve analysis found a best cut-off point of 31 Kg for male and of 19 Kg for female in subjects aged ≥65, while the cut-offs were higher (24 for female and 39 for male) for younger patients (aged < 65 years) as expected. We focused our attention in a large population of patients with cardiac disease where the predictive role of grip strength is assessed in terms of cardiac endpoints. We confirmed that grip strength is associated with mortality (all-cause and cardiac) in patients with cardiac disorders. Heart failure seems to play a major role in this association. It is well known that patients with HF are often affected by cachexia, weakness and frailty [8]. In our study the average BMI was 29 kg/m² and thus in the overweight range. This finding might suggest that overweight and obesity may mask sarcopenia and weakness. Therefore, only a more direct measure of muscle weakness (e.g. grip strength) can improve the identification of subjects at higher risk of hard events.

There is a great interest in the assessment of frailty in cardiac patients [1]. This clinical need is mainly related to the increased number of frail patients that usually are also older [1]. The prevalence of HF reaches 10% among patients aged 70 years and older [24]. The prevalence of frail patients affected by HF is expected to increase, because of the spread of invasive procedures, starting from cardiac revascularization to the percutaneous procedures for the treatment of valvular disease [25]. Frailty syndrome includes weakness, slowness, low level of physical activity, low energy or self-reported exhaustion and unintentional weight loss [26]. Frailty is a geriatric syndrome that reflects a state of decreased physiological reserve and increased vulnerability to stress [26]. In daily clinical practice, the decision between a highly invasive approach and a more conservative treatment strategy, are mainly based on scores like The European System for Cardiac Operative Risk Evaluation (EuroSCORE) II and Society of Thoracic Surgeons (STS) [27]. Both these scores are tailored on clinical variables mainly related to the presence of comorbidities (e.g. age, PAD, creatinine clearance, chronic lung disease, previous cardiac surgery, left ventricle ejection fraction, pulmonary intervention, etc.). Despite the availability of several standardised measures of physical strength and mobility, only one item of these scores is related to an approximate description of the functional status (e.g. severe impairment of mobility secondary to musculoskeletal or neurological dysfunction) [27] without a specification of the kind of test to be used. The major drawback for the daily application of the scales assessing physical performance is that they tend to be too long and complex [28]. They require a specific preparation, a dedicated staff and are time-consuming. Grip strength, as well as other scales, show several limitations. Nevertheless, it has the strong advantage to be easy, user-friendly and quick. In addition, it can be performed also in bedridden patients [29]. Thus, grip strength may be an optimal first choice in the attempt to introduce the assessment of physical performance in the clinical decision-making process of patients with cardiac disorders. Obviously, these speculations

need confirmation and future randomized-controlled clinical trials are clearly in demand [28]. Grip strength is a well characterized measure of weakness and poor muscle performance. Grip strength measures the strength of contraction of the flexor muscles of the fingers/forearm through the use of a dynamometer [5]. From the literature, it is known as such index correlates with the nutritional status of subjects and their capacity for functional recovery post-surgery [26]. In the Prospective Urban-Rural Epidemiology (PURE) study, a large, longitudinal population study, during a median follow-up of 4 years and in a population of 142861 recipients, grip strength was a stronger predictor of all-cause and cardiac mortality than systolic blood pressure [30]. It also showed that every 5 kg decline in grip strength was associated with a 7% increased risk of heart attack, and a 9% higher risk of stroke. The present individual patient pooled meta-analysis included 23481 patients affected by cardiac disorders, confirming that grip strength is a good predictor of cardiac death and hospital admission for heart failure, as well as of all cause death. We are not able to confirm the association with MI and CVA. The population enrolled in the PURE study was bigger. We may not exclude that a larger prospective study on cardiac patients may give different results. At the same time, we cannot define the mechanism behind these associations. We may suppose that endothelial dysfunction, arterial stiffness and autonomic imbalance might mediate the association between muscle strength and cardiovascular events [30]. Nevertheless, further research is needed to solve this issue.

Study limitation

This is an individual patient pooled meta-analysis and data were obtained retrospectively by each corresponding author. For this reason, bias related to incomplete data reporting cannot be excluded. Exclusion criteria of patients were different among studies. We cannot exclude the presence of bias related to the inclusion of patients with arthritis or invaliding stroke for

all the study involved (Table 1). It is important to highlight that the large part of the patients included in the current analysis was retrieved from the study of Celis-Morales [12]. The analysis of the heterogeneity showed a mild degree for cardiac death and an insignificant degree for all-cause death and hospital admission for heart failure. Then, the overall consistency of our analyses and findings is good and we may suppose that the mild degree of heterogeneity is mainly related to the different way to adjudicate cardiac death between trials (Table 1). The multivariate analysis in each single study was slightly modified, based on the clinical variables available for each single study (Table 2s). Finally, it was not possible to perform a pooled survival analysis because data about time-to-event were not available for each single patient.

Conclusions

Grip strength emerged as independent predictor for cardiac death, all-cause death and hospital admission for heart failure in patients with cardiac disorders. In the context of a comprehensive clinical evaluation process, grip strength can support the clinical decision-making process.

DECLARATIONS

Ethics approval and consent to participate

Every study included in the meta-analysis has been published after the approval of an ethic committee and each patient enrolled signed an informed consent. For this reason, the present meta-analysis does not require further ethic committee approval.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Conceived and designed the research: Rita Pavasini, Gianluca Campo, Carlos Celis-Morales. Acquired the data: Matteo Serenelli, Elisabetta Tonet, Giulia Bugani. Performed statistical analysis: Gianluca Campo, Rita Pavasini, Matteo Serenelli. Drafted the manuscript: all authors. Made critical revision of the manuscript for key intellectual content: all authors.

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None

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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FIGURE LEGEND

Figure 1: Outline of the search strategy

Figure 2: Forest plot of the relationship between grip strength (5xKg) and cardiac death.

Data are displayed as OR (95% CI). CI: confidence interval.

Figure 3: Forest plot of the relationship between grip strength (5xKg) and all-cause death.

Data are displayed as OR (95% CI). CI: confidence interval.

Figure 4: Forest plot of the relationship between grip strength (5xKg) and hospital admission for heart failure.

Data are displayed as OR (95% CI). CI: confidence interval. HF: heart failure.

Table 1: Studies included in the meta-analysis

References	Pts	Geographic area	Time and type of the enrolment	Exclusion criteria	Source for documentation of events	CD definition	Major cardiac disease at the inclusion in the study	FU in days	Grip strength
<i>Celis-Morales et al. 2016</i>	22219	England and Wales	April 2007 - December 2010 Prospective	NS. Some patients did not perform grip strength because of undefined illness.	Death certificates Hospital admission identified via record linkage to health episode statistics records	ICD 10 codes I21, I21.4 and I21.9.	Ischemic heart disease and heart failure as defined by the ICD 10 codes I21, I21.4 and I21.9	1538 ±566	Jamar J001005 hydraulic hand dynamometer, mean of the right-hand and left-hand values, expressed as kg.
<i>Colin-Ramirez et al. 2012</i>	396	Mexico	NS Retrospective	Uncontrolled thyroid disorders, hepatic failure, suspicion of tumoral activity, limb amputations, or ischemic heart disease susceptible to revascularization.	Heart failure clinical registry and medical records	Sudden, progressive HF, cardiac arrhythmias, stroke, or myocardial infarction death.	HF: decreased systolic and diastolic function determined at the echocardiography	1332±700	Smedley Hand Dynamometer. Dominant hand. The measurements were repeated twice, and the highest score was recorded in kilograms.
<i>Izawa et al. 200.</i>	147	Kawasaki, Japan	September 1999 - July 2006 Prospective	Heart Association functional class IV, neurologic, peripheral vascular, orthopedic, or pulmonary disease.	Inpatients medical records	Sudden cardiac death, progressive heart failure.	HF: LVEF<45%	495±173	Handle Jamar dynamometer. Average of the highest value of the right + left side handgrip strength/ 2. The highest value measured was considered the index of handgrip strength.
<i>Izumiya et al. 2016</i>	119	Kumamoto, Japan	March 2012 - April 2013 Retrospective	Acute coronary syndrome, malignant tumors, acute infection, chronic hemodialysis and inflammatory diseases.	Medical records	Death related to HF events.	HF: clinical diagnosis according to typical symptoms and signs	337±233	Handgrip strength dynamometer. Two measurements of grip strength of the dominant hand, the higher value of the two measurements was used
<i>Macdonald et al. 2016</i>	145	Sydney, Australia	From March 2013 Prospective	Because already received ventricular assist device or heart transplantation.	NS	NA	HF: advanced heart failure NYHA III or IV	365	Jamar dynamometer. Standard protocol was followed as described by the American Society of Hand Therapy.
<i>McNallan et al. 2013</i>	224	Minnesota, USA	From 2007-2011 Prospective	NS	Rochester Epidemiology project Medical records, death certificates	CD and non-CD death defined according AHA categories	HF diagnosis via Framingham criteria	700±123	Jamar dynamometer
<i>Sancho et al. 2014</i>	330	Valencia, Spain	October 2010 - February 2012 Prospective	Surgical patients.	outpatients' department direct contact, general physician regional registry of mortality	CD was defined as death attributed to cardiac cause or unknown cause.	IHD: acute coronary syndrome.	1788±90	Hand-held isometric dynamometer

Pts: number of patients in the study. CD: cardiac death. FU: follow-up. HF: heart failure. NS: not specified. ICD: international classification of diseases. LVEF: left ventricle ejection fraction. NYHA: New York Heart Association. AHA: American Heart Association. ECG: electrocardiogram.

Table 2: Study population characteristics

	All (n=23480)	CD (n=523)	free from CD (n=22957)	p1	all-cause death (n=2206)	free from all-cause death (n=21274)	p2	Hospitalized for HF (n=887)	free from HF (n=22370)	p3
Age, years	62.3±6.9	68.5±10	62.2±7	< 0.0001	65±8	62±7	<0.0001	63±10	62±7	0.08
Male, n. (%)	16540 (70)	395 (2)	16045 (98)	0.010	1704 (10)	14836 (90)	< 0.0001	717 (33)	15688 (67)	< 0.0001
Height, cm	169±9	168±10	169±9	0.001	169±9	169±9	0.769	168±9	169±9	0.156
Weight, Kg	84±16.8	81±20	84±16	0.001	84±18	84±16	0.937	82±21	84±17	0.008
BMI, Kg/m ²	29±5	29±6	29±5	0.032	29±6	29±5	0.681	28±6	29±5	0.003
Risk factors, n. (%)										
Hypertension	1267 (5)	148 (13)	992 (87)	< 0.0001	308 (24)	959 (76)	< 0.0001	210 (20)	857 (80)	< 0.0001
Current or former smoker	14091 (60)	263 (2)	13828 (98)	0.001	1443 (10)	12648 (90)	< 0.0001	378 (3)	13690 (97)	0.322
Cardiac disease at the inclusion, n (%)										
IHD	11619 (49.5)	335 (3)	11243 (97)	< 0.0001	1330 (11)	10289 (89)	< 0.0001	514 (4)	11105 (96)	< 0.0001
Comorbidities, n. (%)										
COPD	1260 (5.4)	61 (5)	1199 (95)	< 0.0001	252 (20)	1008 (80)	< 0.0001	66 (5)	1145 (95)	< 0.0001
Previous CVA	553 (2.4)	89 (16)	464 (84)	< 0.0001	148 (27)	405 (73)	< 0.0001	33 (6)	520 (94)	< 0.0001
Grip strength, Kg	31±11	27±12	31±11	< 0.0001	29±11	31±11	< 0.0001	30±11	31±11	0.189

CD: cardiac death. HF: heart failure. BMI: body mass index. IHD: ischemic heart disease. COPD: chronic obstructive pulmonary disease. CVA: cerebrovascular accident.

p1: for the comparison between patients reaching or not the endpoint CD. p2: for the comparison between patients reaching or not the endpoint all-cause death. p3: for the comparison between patients reaching or not the endpoint hospital admission for HF.

Table 3: Multivariate logistic regression (individual patient pooled meta-analysis)

	Cardiac death			All-cause death			Admission for HF			Myocardial infarction			Cerebrovascular accident		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Age	1.10	1.08-1.12	<0.001	1.06	1.06-1.08	<0.001	1.04	1.02-1.05	<0.001	1.01	1-1.02	0.001	1.11	1.06-1.16	<0.001
Male	2.19	1.58-3.04	<0.001	2.21	1.9-2.55	<0.001	3.2	2.5-4.08	<0.001	2.05	1.67-2.52	<0.001	--	--	--
BMI	0.86	0.73-1.02	0.083	--	--	--	0.88	0.84-1.02	0.233	--	--	--	--	--	--
Hypertension	3.01	2.10-4.32	<0.001	1.78	1.42-2.23	<0.001	2.83	2.12-3.79	<0.001	2.38	1.79-3.18	<0.001	2.88	1.16-7.10	0.02
Smoking habitus	1.24	0.99-1.56	0.061	1.67	1.5-1.87	<0.001	--	--	--	1.17	1.02-1.34	0.026	0.94	0.51-1.71	0.831
IHD	2.01	1.61-2.51	<0.001	1.63	1.48-1.80	<0.001	1.47	1.26-1.73	<0.001	1.39	1.21-1.59	0.041	1.99	1.08-3.57	0.020
COPD	1.46	1.05-2.05	0.025	1.96	1.67-2.31	<0.001	1.47	1.12-1.93	<0.001	--	--	--	2.4	1.18-4.5	0.016
Previous CVA	7.4	5.62-9.79	<0.001	2.95	2.40-3.60	<0.001	1.29	0.88-1.88	0.877	1.52	1.10-2.11	0.011	--	--	--
Handgrip 5x	0.84	0.79-0.89	<0.001	0.87	0.85-0.89	<0.001	0.88	0.84-0.92	<0.001	0.96	0.92-1	0.06	0.94	0.83-1.07	0.377

HF: heart failure. BMI: body mass index. IHD: ischemic heart disease. COPD: chronic obstructive pulmonary disease. CVA: cerebrovascular accident







