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*a systematic review and meta-analysis*

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## SYSTEMATIC REVIEW

# Preprocedural muscle strength and physical performance and the association with functional decline or mortality in frail older patients after transcatheter aortic valve implementation: a systematic review and meta-analysis

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## Abstract

**Background:** A significant number of older patients planned for transcatheter aortic valve implantation (TAVI) experience a decline in physical functioning and death, despite a successful procedure.

**Objective:** To systematically review the literature on the association of preprocedural muscle strength and physical performance with functional decline or long-term mortality after TAVI.

**Methods:** We followed the PRISMA guidelines and pre-registered this review at PROSPERO (CRD42020208032). A systematic search was conducted in MEDLINE and EMBASE from inception to 10 December 2021. Studies reporting on the association of preprocedural muscle strength or physical performance with functional decline or long-term (>6 months) mortality after the TAVI procedure were included. For outcomes reported by three or more studies, a meta-analysis was performed.

**Results:** In total, two studies reporting on functional decline and 29 studies reporting on mortality were included. The association with functional decline was inconclusive. For mortality, meta-analysis showed that low handgrip strength (hazard ratio (HR) 1.80 [95% confidence interval (CI): 1.22–2.63]), lower distance on the 6-minute walk test (HR 1.15 [95% CI: 1.09–1.21] per 50 m decrease), low performance on the timed up and go test (>20 s) (HR 2.77 [95% CI: 1.79–4.30]) and slow gait speed (<0.83 m/s) (HR 2.24 [95% CI: 1.32–3.81]) were associated with higher long-term mortality.

**Conclusions:** Low muscle strength and physical performance are associated with higher mortality after TAVI, while the association with functional decline stays inconclusive. Future research should focus on interventions to increase muscle strength and physical performance in older cardiac patients.

**Keywords:** cardiac patients, physical performance, muscle strength, functional decline, mortality, systematic review, older people

## Key Points

- A meta-analysis showed that low preprocedural muscle strength and physical performance are associated with mortality after transcatheter aortic valve implantation (TAVI).
- The association between preprocedural muscle strength or physical performance with functional decline stays inconclusive
- Future research should develop interventions to increase muscle strength and physical performance in older cardiac patients.

## Introduction

Approximately 3.4% of adults older than 75 years suffer from severe aortic stenosis [1]. For frail and older patients (>75 years), the less invasive transcatheter aortic valve implantation (TAVI) is the preferred treatment. Even when the TAVI procedure is technically successful, the average mortality beyond 30 days remains approximately 10% in the first year [2]. Furthermore, 30% of the patients experience a decline in physical functioning within 6 months after TAVI [3]. Identifying modifiable factors associated with these adverse outcomes may generate insights to improve current care.

One of the underlying conditions possibly related to negative clinical outcomes is sarcopenia, the multifactorial loss of muscle strength, muscle mass and muscle function [4–6]. The main factors associated with sarcopenia are older age, physical inactivity, poor dietary intake and disease [5]. With effective strategies to improve dietary intake and physical activity, it is possible to prevent or delay the onset of sarcopenia or treat this condition [7–9]. Since many TAVI patients are older, at risk of malnutrition and physically inactive, this could be an effective treatment strategy in this patient group [10, 11]. However, the association between muscle strength, the primary indicator of sarcopenia and adverse long-term outcomes after TAVI remains inconclusive. Current evidence is based on many smaller studies or studies with strength as a secondary outcome, which requires careful interpretation [12]. For the same reason, the association between physical performance and long-term negative outcomes after TAVI is unclear. The main aim of the present study is to systematically review the current literature and perform a meta-analysis to examine if preprocedural muscle strength or physical performance is associated with functional decline or mortality after TAVI.

## Methods

This study followed the PRISMA guidelines for reporting (2020-version) (Supplemental Table 1) [13]. The protocol of this study was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020208032) [14].

### Search strategy and selection criteria

An information specialist (J.L.) performed a systematic search in OVID MEDLINE and OVID EMBASE from

inception onwards to 10 December 2021, using thesaurus terms (i.e. MeSH-terms in MEDLINE) and free text terms for ‘TAVI’, ‘muscle strength’ and ‘physical performance’ (Supplemental Table 2). Reference lists and articles cited were cross-checked for additional relevant studies using Web of Science.

Eligible studies needed to adhere to the following inclusion criteria: (i) they were peer-reviewed original research articles of observational or interventional studies, (ii) participants were TAVI patients, (iii) muscle strength and/or physical performance tests were objectively and preprocedural performed and (iv) mortality and/or functional decline were determined at least 6 months after TAVI as an outcome. Screening, selection and data extraction were all independently performed by two authors (D.v.E. and C.D.D.). In case of disagreement, consent was achieved by discussion or arbitration by a third author (J.D.S.).

### Data extraction

Data were extracted with a data extraction form. The following data were collected: first author, title, year, country, sex ratio, age, sample size, the Society of Thoracic Surgeons risk score, New York Heart Association class, transfemoral access route, follow-up time, mortality, type of functional measurement, physical functioning, type of physical performance or strength test, average muscle strength or physical performance, (adjusted) odds ratios (ORs), hazard ratios (HRs) and event rates with 95% confidence intervals (CIs). When multiple unadjusted and adjusted results were reported on the same muscle strength or performance test, the most adjusted result was extracted. Unclear or missing data were not included in the analysis.

### Quality assessment

The modified Newcastle-Ottawa scale (NOS) for cohort studies was used as a risk of bias assessment [15]. Two authors (D.v.E. and C.D.D.) independently rated the included studies, and disagreements were solved by discussion. The NOS consists of three themes, and a maximum of nine points could be scored. Studies were divided into low risk of bias (score 7–9), high risk of bias (score 4–6) or very high risk of bias (score 0–3) [16]. The quality of evidence was assessed with the grading of recommendations assessment, development and evaluation (GRADE) according to guidelines for research on prognostic factors [17]. GRADE assessment was performed by one researcher (D.v.E.) and checked by

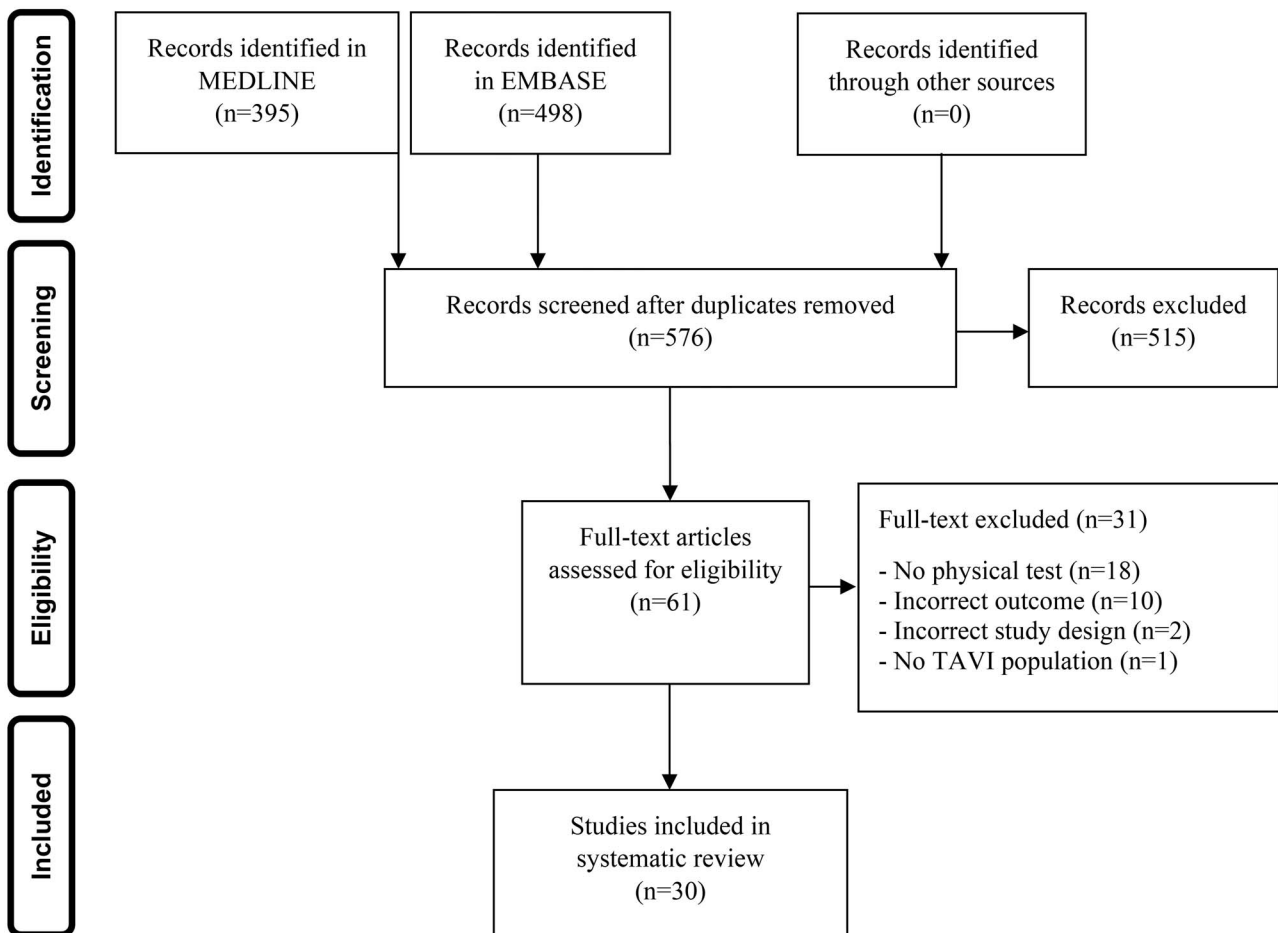


Figure 1. Flow diagram.

another (C.D.D.). The starting rate was high-quality evidence, which was downgraded by one or two levels depending on risk of bias, inconsistency, indirectness, imprecision or publication bias. It was also possible to upgrade the quality of evidence when a large/moderate effect size was present (Supplemental Tables 5–10).

### Statistical analysis

Results were organised by type of muscle strength or physical performance test, outcome and scale (categorical or continuous). When possible, OR was converted to RR and categorical risk data were converted to continuous risk data [16,18]. When three or more studies with unique enrolment reported on the same muscle strength or muscle performance test, a pooled estimate of HR and RR was calculated [18]. When studies had an overlap in enrolment, the study with the largest number of participants was included. HR and RR were assumed to approximate the same measure [19]. Sensitivity analyses were performed, excluding extreme outliers and studies with RR (see Supplemental Figures 1 and 2), or unadjusted studies (see Supplemental Figures 3 and

4). Data were prepared according to the Cochrane handbook [20]. For the meta-analysis, a random-effects model was used with the Paule and Mandel method [21]. Heterogeneity was calculated using the chi-square test and by more than five studies on the same outcome reporting bias was explored with funnel plots. R version 3.6.0 was used for analysis, and a two-sided  $P$ -value of  $<0.05$  was considered significant.

## Results

### Search and selection

The search identified 576 unique articles, of which 515 were excluded based on pre-defined exclusion criteria. Finally, 30 articles were included (Figure 1).

### Study characteristics and quality assessment

All included studies were observational and published between 2012 and 2020 (Table 1). Several studies had an overlap in enrolled patients [3, 22–33]. Unique enrolment for the included studies was  $n = 35,064$ . The average age

**Table 1.** Study characteristics

Study (year) <sup>Ref</sup>	Country	<i>n</i>	Female (%)	Age (years)	BMI (kg/m <sup>2</sup> )	STS-score (%)	Physical test(s)	Outcome	NOS score
Afilalo (2017) [37]	Canada, USA, France	646	46	84 [80–88]	26 [23–29]	5.4 [3.6–8.1]	SPPB	Mortality	7
Altisent (2017) [3]	Canada	305	54	79 ± 9	27 ± 5	6.7 ± 4.2	6MWT	Mortality	8
Assmann (2016) [38]	Netherlands	89	57	80 ± 6	27 ± 5	–	TUGT, GS	Mortality	7
Boureau (2015) [39]	France	150	44	84 ± 5	–	7.2 ± 3.7	TUGT	Mortality/FD	9
Brouessard (2021) [40]	France	182	50	84 [81–86]	26 [24–30]	–	GS	Mortality	7
Chauhan (2016) [41]	USA	342	52	82 ± 7	28 ± 7	7.7 ± 4.6	HG, GS	Mortality	7
Dziewierz (2017) [27]	Poland	148	62	82 [77–85]	27 [25–31]	6.2 [4.0–17.3]	GS	Mortality	8
Eichler (2017) [11]	Germany	333	56	81 ± 5	–	–	TUGT	Mortality	9
Forcillo (2017) [42]	USA	361	46	82 [76–86]	27 [23–30]	9.2 [6.5–12.1]	HG, GS	Mortality	7
Fukui (2020) [43]	Japan	257	34	84 ± 5	22 ± 4	7.0 ± 4.4	GS	Mortality	8
Goudzwaard (2019) [32]	Netherlands	213	54	82 [78–86]	26 [24–30]	–	HG, TUGT, GS	Mortality	7
Goudzwaard (2021) [33]	Netherlands	376	50	82 ± 6	27 ± 5	5.5 ± 3.0	GS	Mortality	9
Green (2012) [24]	USA	159	50	86 ± 8	25 ± 6	11.9 ± 3.9	HG, GS	Mortality	6
Green (2013) [44]	USA	484	46	85 ± 7	26 ± 6	11.1 ± 3.0	6MWT	Mortality	7
Green (2015) [25]	USA	244	52	86 ± 7	25 ± 5	10.9 ± 2.9	HG, GS	Mortality	5
Hermiller (2016) [35]	USA	2,482	46	83 ± 8	–	9 ± 5	HG, GS	Mortality	5
Kagase (2018) [30]	Japan	927	70	–	–	6.7 [4.6–9.4]	HG	Mortality	8
Kano (2017) [29]	Japan	1,256	71	–	22 ± 4	7.9 ± 3.6	GS	Mortality	9
Kiani (2020) [31]	USA	23,605	48	83 [78–88]	–	6.0 [4.1–9.0]	GS	Mortality	7
Kleczynski (2017) [26]	Poland	101	60	81 [76–84]	28 [25–31]	12.0 [5.0–24.0]	GS	Mortality	7
Kure (2022) [36]	Japan	280	69	84 [81–87]	22 [20–25]	6.8 [4.8–9.1]	HG, GS	Mortality	6
Mok (2013) [28]	Canada	212	54	79 ± 9	–	7.0 [4.0–8.6]	6MWT	Mortality	8
van Mourik (2019) [45]	Netherlands, Italy, Canada	71	62	85 ± 3	25 ± 3	5.8 ± 3.9	SPPB	Mortality	8
Saitoh (2020) [46]	Japan	463	71	85 [82–88]	22 [20–25]	5.6 [3.8–7.6]	SPPB	Mortality	7
Sathanathan (2020) [10]	Canada, USA	2037	42	82 ± 7	–	5.6 ± 1.7	6MWT	Mortality	9
Schoenenberger (2012) [34]	Swiss	119	56	83 ± 5	26 ± 5	6.4 ± 3.5	TUGT	FD	6
Schoenenberger (2018) [22]	Swiss	330	56	84 [81–87]	25 [23–28]	6.0 [4.3–8.6]	TUGT	Mortality	8
Steinvil (2018) [47]	USA	498	51	82 ± 8	29 ± 9	7.5 ± 5.1	HG, GS	Mortality	9
Stortecky (2012) [23]	Swiss	100	60	84 ± 5	26 ± 5	6.3 ± 3.3	TUGT	Mortality	8
Van de Velde van De Ginste (2020) [48]	Belgium	125	53	85 ± 5	26 ± 5	5.0 ± 3.1	HG, CST, SPPB, TUGT, GS	Mortality	7

HG, handgrip strength; GS, gait speed; FD, functional decline.

of the participants was between 79 and 86 years. Quality assessment with NOS scores showed five studies with a high risk of bias [24, 25, 34–36].

### Functional decline

Two studies with functional decline as an outcome were identified, both with TUGT as a predictor. In the study by Schoenenberger *et al.* [34], functional decline was described as a decline in one of five daily self-care tasks, which was present in 21% of the patients at 6 months. On the categorical scale, the study showed no association between TUGT (>20 s) and functional decline (unadjusted RR 2.07 [0.97–4.42]). However, on the continuous scale, a significant association was seen (unadjusted RR 1.06 [1.02–1.10] per 1-s increase). The study by Boureau *et al.* [39], measured physical functioning with the Lawton IADL; 31% of the patients experienced a decline in physical functioning at 6 months. This study also showed no association with functional decline

on the categorical scale (adjusted RR 1.26 [0.72–2.22] >20s on TUGT).

### Mortality

#### Muscle strength

Two muscle strength tests were found: the chair stand test (CST) and handgrip strength (Figure 2, Supplemental Table 3).

CST in one study was significantly associated with 1-year mortality. The quality of evidence was low.

Handgrip strength was measured in 10 studies. Meta-analysis showed that lower handgrip strength was significantly associated with mortality on the categorical scale (HR 1.80 [95% CI: 1.22–2.63]) and the continuous scale (HR 1.03 [95% CI: 1.01–1.05] per 1 kg decrease). The quality of evidence was moderate on both scales.

### Physical performance

Four physical performance tests were found: the short physical performance battery (SPPB), the 6-minute walk test (6MWT), the timed up and go test (TUGT) and gait speed (Figure 3 and Supplemental Table 4).

For SPPB, three studies found a significant association [37,46,48]. For the 6MWT, on the continuous scale, a meta-analysis showed a significant association with long-term mortality (HR of 1.15 [95% CI: 1.09–1.21]). The quality of evidence was high.

*TUGT* was performed in seven studies. Meta-analysis showed a significant association between a slow *TUGT* score and mortality (HR 2.77 [95% CI: 1.79–4.30]). On the continuous scale, meta-analysis also showed a significant association (HR 1.06 [95% CI: 1.04–1.09] per 1 s increase). Quality of evidence was moderate.

*Gait speed* was reported in 17 studies. On the categorical scale, eight studies were included in the meta-analysis, which showed a significant association between slow gait speed and mortality (HR was 2.24 [95% CI: 1.32–3.81]). On the continuous scale, seven studies were included in the meta-analysis, which also showed a significant association between gait speed and mortality (HR 1.45 [95% CI: 1.18–1.78] per 0.2 m/s decrease). The quality of evidence was moderate for the categorical scale and high for the continuous scale.

### Discussion

Our meta-analysis revealed that preprocedural lower strength (handgrip) and physical performance (6MWT, *TUGT* and gait speed) were associated with higher long-term mortality. The quality of evidence for these associations was moderate for muscle strength and moderate to high for physical performance. Since only two studies were performed with a decline in physical functioning as an outcome, this association remains inconclusive.

In our study, low preprocedural handgrip strength and low physical performance were strongly associated with higher mortality after TAVI. The association between low handgrip strength and mortality after TAVI had an HR of 1.80 [95% CI: 1.22–2.63]. This appears to be higher than in healthy older adults in two previously performed meta-analyses (HR 1.45 [95% CI: 1.35–1.56] and 1.41 [95% CI: 1.30–1.52]) [49,50]. However, the results were comparable to older adults with a chronic or acute disease (HR of 1.80 [95% CI: 1.54–2.10]) [51]. This indicates that muscle strength is associated with mortality, especially in periods of disease. Similar results were seen for physical performance. A meta-analysis of nine studies in healthy older adults showed an HR of 1.29 [95% CI: 1.23–1.32] per 0.2 m/s decrease in gait speed [52]. This is somewhat lower than the HR of 1.45 [95% CI: 1.18–1.78] per 0.2 m/s decrease in gait speed found in our study. Preprocedural screening, therefore, seems to be an important moment to diagnose low muscle strength

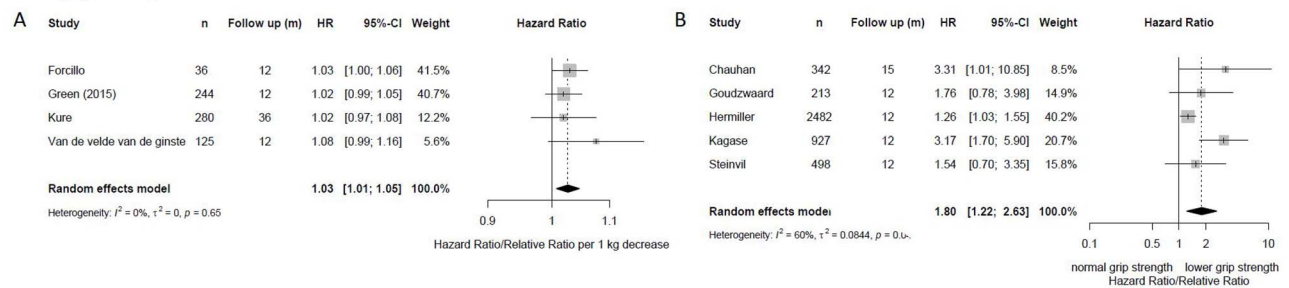
or low physical performance and to initiate interventions to improve strength and performance.

With the current body of evidence, a relationship between preoperative strength and physical performance with functional decline after TAVI could not be concluded. Although longevity is an important outcome for many patients, it is not the only reason for patients to undergo the TAVI procedure [53]. Because a vast majority of TAVI patients have a high age and experience burdens from comorbidities, improving physical functioning is of similar importance [53–55]. It is relevant to study the association between muscle strength, physical performance and functional decline because it could be a meaningful motivator for patients and healthcare professionals to initiate interventions.

Our results have important implications for research and clinical practice. Current guidelines already recommend measurement of physical performance as part of the screening before TAVI [56]. Results from this study can be used to better predict outcomes. Our results additionally highlight that measurement of muscle strength should be recommended, in accordance with the guidelines for sarcopenia [4]. When low muscle strength or low physical performance is present, these conditions can be improved with exercise training and nutrition interventions, even in a relatively short time span of 8 weeks [57]. The combination of resistance exercise training, aerobic training, sufficient protein intake and good diet quality has shown to effectively increase muscle strength and physical performance [57–60]. However, due to frailty, old age and symptoms of severe aortic stenosis, currently available interventions do not immediately apply to the TAVI population [61]. Creative solutions are warranted to increase feasibility, adherence and motivation in this patient group. These might include technology-supported home-based interventions, functional training with a physiotherapist or involvement of a training buddy [61,62]. Furthermore, it is currently unknown if improved muscle strength and physical performance also lead to better long-term outcomes in this older and frailer patient population [63].

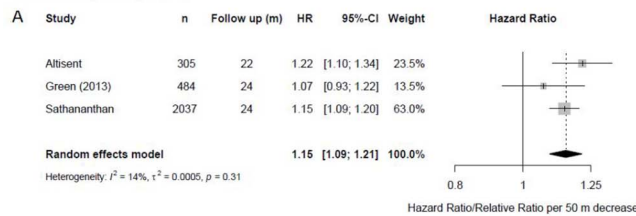
Our study has several strengths and limitations. It is the first study to show an association of muscle strength and multiple physical performance tests with mortality after TAVI. Furthermore, the latest PRISMA guidelines were followed, and the quality of evidence was rated according to the GRADE guidelines. The first limitation is that most meta-analyses showed significant heterogeneity, which was probably caused by differences in cut-off values or follow-up time. This could have led to wide confidence intervals and underestimation of the association relative to the best possible cut-off points. Second, a meta-analysis could only be performed on a limited number of studies because of a wide variety of tests, scales and outcomes. The small number of studies made it impossible to perform subgroup analysis or more analysis to test the robustness of the results.

Handgrip strength

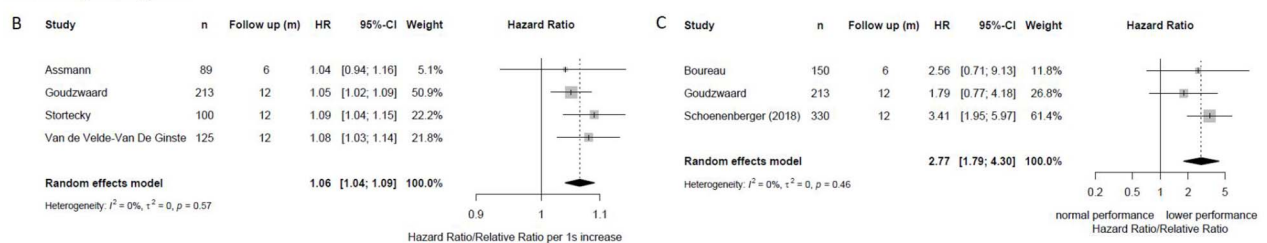


**Figure 2.** Forest plots for muscle strength and the association with mortality. Left: Continuous; right: dichotomous; m: months. (A) Continuous handgrip strength (per 1 kg). (B) Dichotomous handgrip strength (low versus normal).

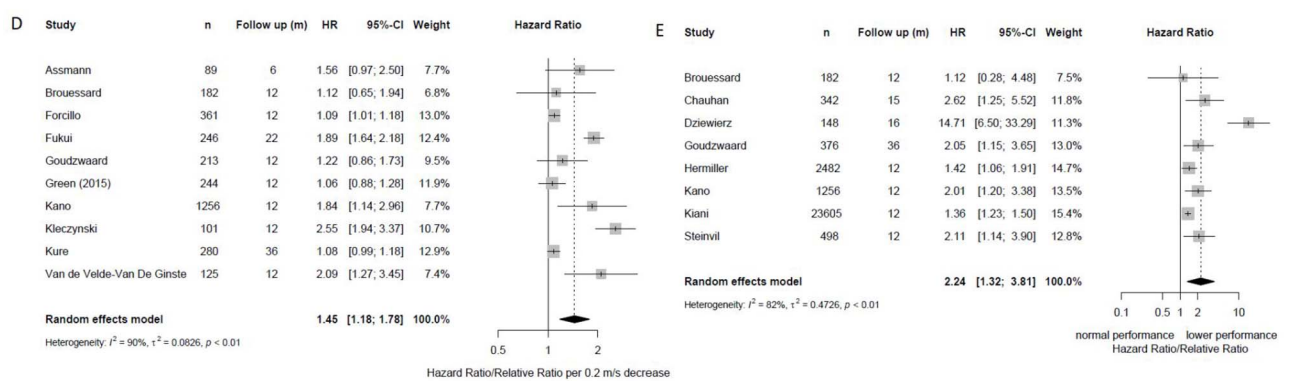
Six-minute walk test



Timed up and go test



Gait speed



**Figure 3.** Forest plots for physical performance and the association with mortality. Left: Continuous; right: dichotomous; m: months. (A) Continuous 6MWT (per 50 m). (B) Continuous TUGT (per 1 s). (C) Dichotomous TUGT (<20 s versus >20 s). (D) Continuous gait speed (per 0.2 m/s), (E) Dichotomous gait speed (slow versus normal).

In conclusion, this systematic review in patients with severe aortic stenosis shows that preprocedural muscle strength and physical performance are associated with long-term mortality after TAVI. The association with functional decline remains inconclusive and is of interest for future research. In addition, future research should focus on the development of feasible and effective interventions for

older patients to improve muscle strength and physical performance before the procedure.

**Acknowledgements:** Availability of study material: Original search data, quality assessment, the data extraction form and syntax used for analysis can be found on Figshare ([doi.org/10.6084/m9.figshare.20347716](https://doi.org/10.6084/m9.figshare.20347716)).

**Declaration of Conflicts of Interest:** None.

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