Gait Speed Can Predict Advanced Clinical Outcomes in Patients Who Undergo Transcatheter Aortic Valve Replacement

Insights From a Japanese Multicenter Registry

Seiji Kano, MD; Masanori Yamamoto, MD; Tetsuro Shimura, MD; Ai Kagase, MD; Masanao Tsuzuki, PT; Atsuko Kodama, MD; Yutaka Koyama, MD; Toshihiro Kobayashi, RT; Kenichi Shibata, PT; Norio Tada, MD; Toru Naganuma, MD; Motoharu Araki, MD; Futoshi Yamanaka, MD; Shinichi Shirai, MD; Kazuki Mizutani, MD; Minoru Tabata, MD; Hiroshi Ueno, MD; Kensuke Takagi, MD; Akihiro Higashimori, MD; Toshiaki Otsuka, MD; Yusuke Watanabe, MD; Kentaro Hayashida, MD

Background—Gait speed reflects an important factor of frailty and is associated with an increased risk of late mortality in patients with cardiac disease. This study sought to assess the prognostic value of gait speed in elderly patients who underwent transcatheter aortic valve replacement.

Methods and Results—We investigated the 5-m or 15-feet gait speed (m/sec) in 1256 patients who underwent transcatheter aortic valve implantation using data from the OCEAN-TAVI Japanese multicenter registry (Optimized Catheter Valvular Intervention–Transcatheter Aortic Valve Implantation). Baseline characteristics, procedural outcomes, and all-cause mortality were compared among groups defined by differential gait speed classification: model 1, normal (>0.83 m/sec; n=563; 44.8%), slow (0.5–0.83 m/sec; n=429; 34.2%), slowest (<0.83 m/sec; n=205; 16.3%), unable to walk (n=48; 3.8%); and model 2, classification and regression tree survival model indicating the threshold of gait speed as 0.385 m/sec (>0.385 m/sec; n=1080 versus ≤0.385 m/sec; n=117). The cumulative 1-year mortality rate showed significant differences in the classical gait speed groups in model 1 (7.6%, 6.6%, 18.2%, and 40.7%, respectively; $P<0.001$) and survival classification and regression tree group in model 2 (7.7% versus 21.9%; $P<0.001$). The slowest walkers and those unable to walk demonstrated independent associations with increased midterm mortality after adjustment for several confounding factors (hazard ratio, 1.83, 4.28; 95% confidence interval, 1.03–3.26, 2.22–8.72; $P=0.039$, <0.001, respectively). Gait speed <0.385 m/sec determined by classification and regression tree also independently associated with worse prognosis (hazard ratio, 2.40; 95% confidence interval, 1.75–5.88; $P=0.001$).

Conclusions—Gait speed using both traditional and specific classification is useful as a potential marker for predicting vulnerable patients associated with adverse clinical outcomes after transcatheter aortic valve replacement. **(*Circ Cardiovasc Interv*. 2017;10:e005088. DOI: 10.1161/CIRCINTERVENTIONS.117.005088.)**

Key Words: foot ■ heart diseases ■ risk ■ transcatheter aortic valve replacement ■ walkers

Recently, the indication for transcatheter aortic valve replacement (TAVR) has been expanded not only to patients with degenerative aortic stenosis considered inoperable or of high surgical risk but also to those with intermediate surgical risk.[1–3] Thus, optimal patient risk stratification should be performed before the TAVR procedure. Frailty, which is not captured in the classical surgical risk model, is considered highly prevalent in elderly vulnerable patients and can be characterized by

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From the Department of Cardiology, Nagoya Heart Canter, Japan (S.K., M.Y., Y.K., T.K., K.S.); Department of Cardiology, Toyohashi Heart Canter, Japan (M.Y., T.S., A. Kagase, M. Tsuzuki, A. Kodama); Department of Cardiology, Sendai Kosei Hospital, Japan (N.T.); Department of Cardiology, New Tokyo Hospital, Chiba, Japan (T.N.); Department of Cardiology, Saiseikai Yokohama City Eastern Hospital, Japan (M.A.); Department of Cardiology, Syonan Kamakura General Hospital, Japan (F.Y.); Department of Cardiology, Kokura Memorial Hospital, Japan (S.S.); Department of Cardiology, Osaka City General Hospital, Japan (K.M.); Department of Cardiovascular Surgery, Tokyo Bay Urayasu Ichikawa Medical Center, Chiba, Japan (M. Tabata); Department of Cardiology, Toyama University Hospital, Japan (H.U.); Department of Cardiology, Ogaki Municipal Hospital, Gifu, Japan (K.T.); Department of Cardiology, Kishiwada Tokushukai Hospital, Osaka, Japan (A.H.); Department of Hygiene and Public Health, Nippon Medical School, Tokyo, Japan (T.O.); Center for Clinical Research, Nippon Medical School Hospital, Tokyo, Japan (T.O.); Department of Cardiology, Teikyo University School of Medicine, Tokyo, Japan (Y.W.); and Department of Cardiology, Keio University School of Medicine, Tokyo, Japan (K.H.).

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Correspondence to Masanori Yamamoto, MD, PhD, FESC, Department of Cardiology, Toyohashi Heart Canter, 21-1 Gobudori, Oyamachyo, Toyohashi, Aichi 441–8530, Japan. E-mail yamamoto@heart-center.or.jp, masa-nori@nms.ac.jp

WHAT IS KNOWN

- Frailty is well known as a geriatric syndrome of impaired resiliency to stressors, which confers a high risk for adverse health outcomes.
- Gait speed is a simple tool for evaluating the degree of frailty and does not require geriatric specialists.
- Gait speed is also a physical functional measure predictive of adverse outcomes and mortality in elderly cohort.

WHAT THE STUDY ADDS

- The present study revealed an increased midterm mortality rate after transcatheter aortic valve implantation in patients with declined gait speed or unable to walk as compared with that for patients with a normal gait speed.
- Gait speed was also significantly correlated with other frailty components, such as grip strength (muscle function), albumin level (nutritional status), Mini-Mental State Examination score, and Clinical Frail Scale score (semiquantitative frailty assessment).
- Gait speed assessment has potential in identifying patients at risk for mortality after transcatheter aortic valve replacement, which would help refine patient selection and further characterize the concept of futility in transcatheter aortic valve replacement candidates.

several phenotypes to enhance the individual patient clinical status.[4] Indeed, strict evaluations of frailty status have been determined using comprehensive geriatric assessments with complex scales determining a frailty index.[5,6] In contrast, gait speed is a simple tool for evaluating the clinical definition of frailty and does not require geriatric specialists. Moreover, a large-scale clinical investigation previously demonstrated a relationship between impaired gait speed and poor survival in older patients.[7] In addition, numerous investigations have demonstrated that gait speed reflects the degree of frailty well and is a useful marker for predicting the early and late clinical outcomes in patients with particular subsets of cardiovascular disease undergoing invasive cardiac surgery.[8–11] Therefore, we investigated the usefulness of gait speed as a frailty measure predicting the prognosis of patients who underwent TAVR procedures using data from a Japanese multicenter registry.

Methods

Study Population

A total of 1613 patients were enrolled in the OCEAN-TAVI registry (Optimized Catheter Valvular Intervention–Transcatheter Aortic Valve Implantation) between October 2013 and April 2016. The OCEAN-TAVI is an ongoing multicenter registry in 14 relatively high-volume centers in Japan.[12–14] Initially, we excluded 262 patients with missing data, 36 patients with a nonelective situation before TAVR, and 59 patients who could not undergo the study examination because of severe clinical symptoms, such as dyspnea or heart failure. Thus, the final sample included the remaining 1256 patients (Figure 1).

Patients were determined to be an adequate candidate for TAVR through the consensus of the individual centers and through discussions within the heart team when considering the surgical risk for those with multiple comorbidities. Surgical risk was considered according to the values of the logistic European system for cardiac operative risk evaluation (EuroSCORE), EuroSCORE II, and the society of thoracic surgeons predictive risk of mortality (STS) score. Clinical data, patient characteristics, laboratory data, echocardiographic data, procedural variables, length of hospital stay, and in-hospital and all-cause mortality rates were examined. The medical ethics committee approved this study in each hospital, and written informed consent was obtained from all patients before the TAVR procedure. Information on the occurrence and causes of death was obtained from the treating hospital or by calling the patient's family member(s).

Gait Speed Assessment

Gait speed was calculated using a 5-m walking test in 14 centers and a 15-feet walking test in 2 centers (Teikyo University and Sendai Kosei Hospital). Technicians at all 14 centers were well trained in conducting the 5-m walk or 15-feet test, from which gait speed was assessed. The test was performed in a well-lit hallway with markings at 0 and 5 m or 15 feet. Patients were instructed to walk at a comfortable speed over the target distance. A standard digital stopwatch was used to calculate the time between the first footfall over the 0 line and the first footfall over the target line (5 m or 15 feet). A cutoff point of 0.83 m/sec has been advocated as defining slow walkers for patients undergoing cardiac surgery,[11] whereas a lower cutoff of <0.5 m/sec has been proposed for patients undergoing TAVR, who are typically older and more functionally compromised.[15,16] Therefore, the patients were categorized into 4 gait speed groups as follows: normal walkers (>0.83 m/sec), slow walkers (0.5–0.83 m/sec), the slowest walkers (<0.5 m/sec), and those unable to walk (model 1). The unable-to-walk group included patients who depended on a wheelchair or almost depended for personal care. The physician made an effort to evaluate the patient's conditions; thus, the unreliable subjects were strictly excluded from the unable-to-walk category. The CART (classification and regression tree) analysis is an empirical and statistical method to create the decision rules based on data rather than speculation and make the risk stratification model.[17] The survival CART analysis identified that an adequate cutoff value of gait speed was 0.385 m/sec. We also divided patients into 2 risk groups (>0.385 m/sec; n=1080 versus ≤0.385 m/sec; n=117) according to the above cutoff value (model 2).

TAVI Procedure and Data Definition

Detailed TAVI procedures have been previously described.[12–14] The Edwards SAPIEN-XT (Edwards; Edwards Lifesciences, Irvine, CA) balloon-expandable prosthesis was first introduced in Japan in October 2013; the Medtronic CoreValve revalving system (Corevalve; Medtronic, Minneapolis, MN) self-expandable prosthesis was used starting in January 2016. The size of the bioprosthesis was determined mainly using multidetector computed tomographic findings or echocardiography, based on the individual center examinations. Approach routes were chosen via the femoral artery first; if the femoral access was inappropriate, the iliac artery, apical, subclavian, or direct aortic routes were considered. Procedural complications, including acute kidney injury, vascular complications, bleeding, and additional complications during TAVR, were evaluated according to the valve academic research consortium-2 criteria.[18] This trial was registered with the University Hospital Medical Information Network (no. UMIN000020423).

Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics v22 (SPSS, Inc, Chicago, IL), R software packages (version 3.0.1; R Development Core team), or Stata v14 (Stata Corp, College Station, TX). Continuous variables are expressed as mean±SD and as medians with interquartile ranges. Group differences were tested using a 1-way analysis of variance or Kruskal–Wallis test depending on the variable's distribution. Spearman correlation analyses were performed to evaluate relationships between gait speed and other traditional frailty components (body mass index, peak grip strength, albumin level,

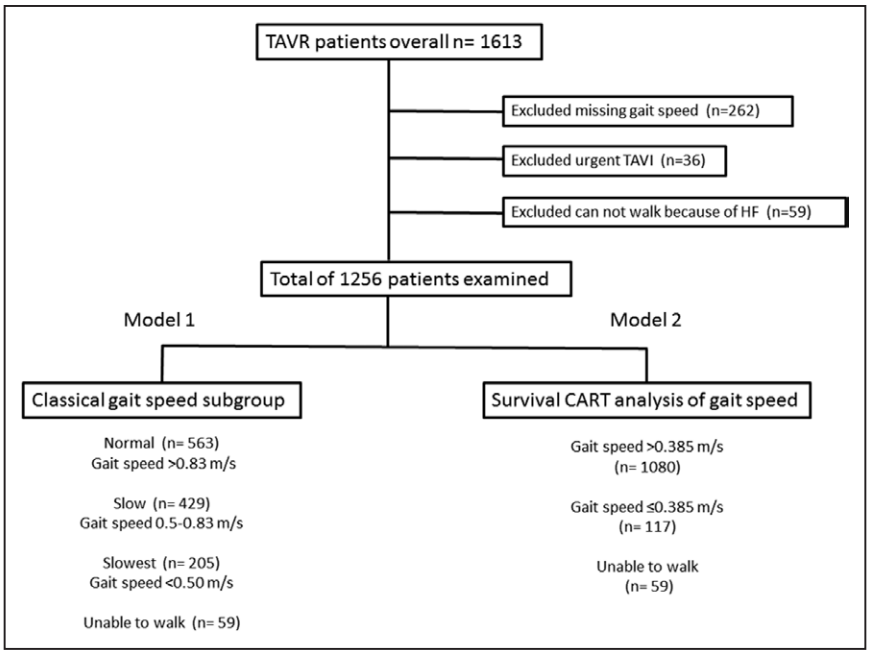

Figure 1. Inclusion flow diagram of study population. CART indicates classification and regression tree; HF, heart failure; and TAVR, transcatheter aortic valve replacement.

Mini-Mental State Examination [MMSE] score, and Clinical Frail Scale [CFS] score). The Kaplan–Meier method was used to estimate the cumulative incidence, and differences were assessed with the log-rank test. In addition, subgroup analyses for traditional surgical risk subsets (STS <4%, 4% to 8%, and >8%), as well as overall, were performed in the transfemoral cohort. A univariable Cox regression analysis was performed to obtain the hazard ratio (HR) for midterm mortality during the follow-up period. Thereafter, a multivariable analysis was performed using the baseline clinical characteristics and other variables with a univariable P value <0.1 to examine independent associations of gait speed classification (models 1 and 2) with midterm mortality. A restricted cubic spline with 5 knots was used to show a continuous relationship between gait speed and adjusted HR for mortality. The locations of the 5 knots were determined as the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the distribution of gait speed. The reference value of gait speed was set at 0.83 m/s, which is traditionally considered as the normal limit. The HR was adjusted for age group, male sex, New York Heart Association class III/IV, diabetes mellitus, previous coronary artery bypass grafting, STS score, B-type natriuretic peptide, serum creatinine, hemoglobin, transfemoral approach, peripheral artery disease, and liver disease. P values <0.05 were considered statistically significant.

Results

Baseline Patient Characteristics and Procedural Variables

Among the 1256 patients, 44.8% were categorized as normal walkers (n=563), 34.2% as slow walkers (n=429), 16.3% as the slowest walkers (n=205), and 4.7% were unable to walk (n=59). Baseline patient characteristics are presented in Table 1. Statistically significant group differences were found for age, sex, body characteristics, the prevalence of New York Heart Association class III/IV, B-type natriuretic peptide value, and other comorbidities. As a result, preoperative risk scores, such as logistic EuroSCORE, EuroSCORE II, and STS score were higher in patients unable to walk. Body mass index, peak grip strength, albumin levels, and MMSE scores were lower, and semiquantitative CFS grade was higher across the 4 groups (all P<0.05). Procedural variables are described in Table 2. The procedure time demonstrated significant group differences (86.4±53.5 minutes versus 87.3±41.2 minutes versus 98.2±54.3 minutes versus 99.5±48.4 minutes, respectively; P=0.033). Significant group differences in the approach route were also found, with the rate for the nontransfemoral approach higher in those unable to walk (19.6% versus 17.1% versus 23.1% versus 39.6%, respectively; P=0.003). In addition, significant group differences were found for the length of hospital stay and intensive care unit stay (P<0.001 and P<0.001, respectively), valve academic research consortium-2–defined acute kidney injury (6.0% versus 6.7% versus 12.2% versus 14.6%, respectively; P=0.021), and life threatening/disabling bleeding (3.8% versus 4.9% versus 11.6% versus 10.4%, respectively; P=0.002). The 30-day mortality rates were not statistically different among groups; however, the 30-day mortality rate was relatively higher in the unable-to-walk group (1.8% versus 1.8% versus 1.4% versus 4.2%, respectively; P=0.66). Concerning about the model 2, baseline patient characteristics are given in Table I in the Data Supplement, and procedural variables are shown in Table II in the Data Supplement. Gait speed was significantly correlated with CFS grade (ρ=0.36; P<0.001), peak grip strength (ρ=0.43; P<0.001), albumin level (ρ=0.25; P<0.001), MMSE score (ρ=0.18; P<0.001), and CFS score (ρ=−0.36; P<0.001). In contrast, body mass index was not associated with gait speed (ρ=−0.004; P=0.88).

Clinical Outcomes in Each Gait Speed Group

All patients were clinically followed for at least 30 days (among survived patients), with a median follow-up duration of 326 days (interquartile range, 102.0–449.8). A total of 116 patients with all-cause death were identified during the follow-up period; 14 patients died within 30 days (12.1%), and the remaining 102 patients (87.9%) died beyond 30 days of the TAVI procedure. The Kaplan–Meier curves demonstrated significant group differences in terms of all-cause mortality (Figure 2). The cumulative 1-year mortality rates among the 4 groups in model 1 were 7.6% for normal walkers, 6.6% for

Table 1. Baseline Characteristics of Study Patients

	Normal Gait Speed, >0.83 m/sec (n=563)	Slow Gait Speed, 0.5–0.83 m/sec (n=429)	Slowest Gait Speed, <0.5 m/sec (n=205)	Unable to Walk (n=59)	*P* Value	*P* Trend
Baseline clinical characteristics						
Age group, y (n), %						
<80	109 (19.4)	53 (12.4)	19 (9.3)	6 (10.2)		
80–84	209 (37.1)	121 (28.2)	57 (27.8)	13 (22.0)	<0.001	<0.001
85–89	198 (35.2)	194 (45.2)	86 (42.0)	26 (44.1)		
≥90	47 (8.3)	61 (14.2)	43 (21.0)	14 (23.7)		
Men (n), %	230 (40.9)	84 (19.6)	37 (18.0)	10 (16.9)	<0.001	<0.001
Height, cm	152.3±9.1	148.2±8.1	146.1±8.9	145.3±14.1	0.001	<0.001
Weight, kg	51.3±10.6	49.0±9.0	48.9±10.3	45.9±17.0	<0.001	<0.001
BSA, m^2	1.5±0.2	1.4±0.1	1.4±0.2	1.3±0.1	0.001	<0.001
BMI, kg/m^2	22.0±3.4	22.2±3.4	22.8±3.9	20.4±3.2	0.26	0.95
BMI <20 (n), %	158 (28.1)	115 (26.8)	47 (22.9)	32 (54.2)	<0.001	<0.001
NYHA class, III or IV, %	225 (40.0)	231 (53.8)	131 (63.9)	39 (66.1)	<0.001	<0.001
Logistic EuroSCORE, %	17.8 (7.9–20.3)	16.8 (9.0–22.2)	17.0 (9.0–21.0)	23.1 (11.2–30.5)	0.001	<0.001
EuroSCORE II, %	4.7 (2.1–5.7)	4.9 (2.4–5.5)	5.3 (2.6–5.8)	8.8 (3.2–8.0)	<0.001	<0.001
STS score (n), %	7.5 (4.3–8.8)	7.8 (4.9–9.1)	8.0 (4.7–9.9)	11.7 (6.0–14.0)	<0.001	<0.001
<4	129 (22.9)	55 (12.8)	28 (13.7)	3 (5.1)	<0.001	<0.001
4–8	266 (47.2)	224 (52.2)	92 (44.9)	18 (30.5)		
>8	168 (29.8)	150 (35.0)	85 (41.5)	38 (64.4)		
Other frailty components						
Peek grip strength (n=1096), kg	18.6±7.6 (n=512)	14.4±6.0 (n=372)	12.3±5.9 (n=174)	6.9±6.6 (n=38)	<0.001	<0.001
Albumin, g/dL	3.9±0.4	3.8±0.4	3.6±0.5	3.3±0.6	<0.001	<0.001
MMSE (n=998)	25.9±5.6 (n=431)	25.3±4.1 (n=358)	23.7±4.8 (n=173)	21.4±6.1 (n=36)	0.024	<0.001
CFS	3.6±1.1	3.9±1.0	4.5±1.1	6.5±1.2	0.015	<0.001
Preprocedural laboratory data						
BNP, pg/mL	316.1 (83.5–427.3)	368.5 (83.3–464.5)	395.9 (64.6–480.4)	654.2 (151.3–679.2)	0.046	0.049
Creatinine, mg/dL	1.0±0.5	1.0±0.5	1.0±0.4	1.1±0.6	0.29	0.75
Estimated glomerular filtration rate, mL/min	53.3±18.7	51.5±19.6	50.6±20.3	51.4±25.9	0.023	0.088
Hemoglobin, g/dL	11.6±1.6	11.2±1.6	10.8±1.6	10.3±1.7	0.99	<0.001
Comorbidities						
Peripheral artery disease (n), %	73 (13.0)	60 (14.0)	40 (19.6)	16 (27.1)	0.006	0.011
Prior MI	40 (7.1)	28 (6.5)	14 (6.8)	4 (6.8)	0.99	0.99
Prior PCI	161 (28.6)	117 (27.3)	49 (23.9)	15 (25.4)	0.62	0.62
Prior CABG	51 (9.1)	35 (8.2)	10 (4.9)	3 (5.1)	0.11	0.15
Prior stroke	71 (12.6)	64 (14.9)	35 (17.1)	11 (18.6)	0.31	0.32
Diabetes mellitus	153 (27.2)	118 (27.5)	48 (23.4)	16 (27.1)	0.72	0.71
Hypertension	453 (80.5)	338 (78.8)	163 (79.5)	39 (66.1)	0.082	0.11
Pulmonary disease	151 (26.9)	111 (25.9)	42 (20.5)	18 (30.5)	0.26	0.25
Liver disease	16 (2.8)	12 (2.8)	13 (6.3)	1 (1.7)	0.071	0.41
Active cancer	40 (7.1)	20 (4.7)	6 (2.9)	2 (3.4)	0.40	0.25

(*Continued*)

Table 1. Continued

	Normal Gait Speed, >0.83 m/sec (n=563)	Slow Gait Speed, 0.5–0.83 m/sec (n=429)	Slowest Gait Speed, <0.5 m/sec (n=205)	Unable to Walk (n=59)	*P* Value	*P* Trend
Echocardiographic data						
LVEF, %	59.5±11.3	60.0±11.8	59.3±11.1	57.0±13.9	0.28	0.35
AVA, cm^2	0.65±0.15	0.62±0.18	0.61±0.17	0.56±0.15	<0.001	<0.001
Indexed AVA, cm^2/m^2	0.44±0.11	0.44±0.13	0.44±0.12	0.41±0.13	0.005	0.044
Peak velocity, m/sec	4.5±0.76	4.5±0.81	4.6±0.87	4.7±0.77	0.28	0.20
Peak gradient, mm Hg	85.0±27.8	84.5±28.6	88.7±31.8	88.8±29.5	0.32	0.13
Mean gradient, mm Hg	50.1±17.7	49.3±17.2	52.0±19.5	53.3±18.6	0.36	0.14
AR ≥moderate (n), %	55 (9.8)	30 (7.0)	31 (15.1)	8 (13.6)	0.010	0.013
MR ≥moderate (n), %	42 (7.5)	41 (9.6)	29 (14.1)	6 (10.2)	0.047	0.058

Values are numbers (%) or mean±SD. AR indicates aortic regurgitation; AVA, aortic valve area; BMI, body mass index; BNP, B-type natriuretic peptide; BSA, body surface area; CABG, coronary artery bypass graft; CFS, clinical scale score; EuroSCORE, European system for cardiac operative risk evaluation; LVEF, left ventricle ejection fraction; MI, myocardial infarction; MMSE, Mini-Mental State Examination; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and STS score, society of thoracic surgeons predictive risk of mortality.

slow walkers, 18.2% for the slowest walkers, and 40.7% for those unable to walk (log-rank test; *P*<0.001). The cumulative 1-year mortality rates among the 2 groups in model 2 were 7.1% for gait speed ≤0.385 m/sec and 21.9% for gait speed >0.385 m/sec (log-rank test; *P*<0.001). Kaplan–Meier curves indicated significant increased cardiovascular mortality rates between the groups in classical gait and survival CART (Figure 3A and 3C). Moreover, noncardiovascular mortality rates tended to show differences between the 2 groups (Figure 3B and 3D). Kaplan–Meier analyses focused on the transfemoral cohort identified significant survival curve differences in the overall, STS 4% to 8%, and STS >8% subgroups. However, the statistical differences were diminished in the STS <4% subgroup because of the small number of patients in the slowest (n=21) and unable-to-walk (n=2) groups (Figure I in the Data Supplement). A subgroup analysis was also performed, dividing patients into transfemoral and nontransfemoral approach subgroups. The subgroup analysis revealed significant differences in mortality based on the gait classification (Figure 2A and 2B in the Data Supplement). The results were not attenuated after the exclusion of patients unable to walk (Figure 2C and 2D in the Data Supplement). The results of the Cox regression analysis models examining the association between all-cause mortality and clinical findings are presented in Table 3 (models 1 and 2). In the univariable Cox regression, gait speed level (model 1) demonstrated a stepwise incremental increase in risk of mortality in the slowest walkers and those unable to walk when compared with that for normal walkers (HR, 2.15, 5.03; 95% confidence interval [CI], 1.33–3.47, 2.78–9.11; *P*=0.002, *P*<0.001, respectively). The results were not diminished even after adjusting for clinical confounding parameters; both the slowest and unable-to-walk groups (model 1) were independently associated with an increased risk of mortality during the follow-up period (HR, 2.01, 3.45; 95% CI, 1.20–3.38, 1.79–6.65; *P*=0.008, <0.001, respectively). In model 2, gait speed <0385 m/sec also showed significant increased risk of mortality after TAVR (HR, 2.40; 95% CI, 1.43–4.05; *P*=0.001). Other clinical findings, including New York Heart Association class III/IV (HR, 1.53; 95% CI, 1.04–2.51; *P*=0.033), baseline serum creatinine value (HR, 1.37; 95% CI, 1.02–1.84; *P*=0.036), baseline serum hemoglobin value (HR, 0.80; 95% CI, 0.70–0.92; *P*=0.002), and the presence of liver disease (HR, 3.79; 95% CI, 1.79–8.00; *P*<0.001), were also independently associated with an increased risk of mortality after TAVI. The baseline STS score, peripheral artery disease, and the transfemoral approach were significant predictive factors for an increased risk of mortality in the univariable analyses, but the relationships were attenuated in the multivariable model. If patients unable to walk are excluded, independent association between impaired gait speed and increased risk of mortality are the same. (Table 4). Increase in risk of mortality in the slowest walkers (<0.5 m/sec) and those <0.385 m/sec were not diminished in the Cox regression multivariable analysis. (HR, 1.84, 2.44; 95% CI, 1.07–3.15, 1.42–4.20; *P*=0.027, 0.001, respectively). Based on a restricted cubic spline, a continuous relationship between gait speed and mortality risk was drawn, using a reference value of gait speed of 0.83 m/sec (Figure 4).

Discussion

The present study demonstrated a stepwise incremental increased risk of mortality after TAVR in patients with the slowest gait speed (<0.5 m/sec) or who were unable to walk compared with that for patients with a normal gait speed. In addition to traditional classification, specific survival CART analysis indicated that gait speed as 0.385 m/sec in this study population was an independent predictive factor of worse prognosis after TAVR. These trends were maintained after adjusting for differences in baseline patient characteristics. Gait speed assessment was also useful in predicting a poor prognosis in patients who underwent transfemoral TAVR. When patients were divided into low (STS <4%), intermediate (STS 4–8), and high (STS >8%) surgical risk groups, significant survival differences based on the gait speed classification were found among patients in the intermediate and high surgical risk groups. However, it was difficult to evaluate statistical differences in the low-risk group because of the extremely small number of patients in the slowest (n=21) and unable-to-walk

Table 2. Procedural Patient Characteristics

	Normal Gait Speed, 0.83 m/sec (n=563)	Slow Gait Speed, 0.5–0.83 m/sec (n=429)	Slowest Gait Speed, <0.5 m/sec (n=205)	Unable to Walk (n=59)	*P* Value	*P* Trend
Procedural variables						
Procedure time, min	84.7±49.8	85.8±41.3	96.2±52.4	92.9±42.0	0.38	0.13
Fluoroscopy time, min	20.1±11.0	20.6±9.9	20.9±10.3	18.7±8.2	0.55	0.85
Contrast medium volume, mL	125.7±51.9	116.4±59.4	119.6±61.2	122.3±51.1	0.18	0.007
Approach route (n), %						
Transfemoral approach	457 (81.2)	350 (81.6)	153 (74.6)	39 (66.1)	0.009	0.013
Nontransfemoral approach	106 (18.8)	79 (18.4)	52 (25.4)	20 (33.9)		
Transapical approach	97 (17.2)	67 (15.6)	46 (22.4)	17 (28.8)		
Transiliac approach	6 (1.1)	12 (2.8)	5 (2.4)	1 (1.7)		
Transaortic approach	3 (0.5)	0 (0)	1 (0.5)	2 (3.4)		
Transsubclavian approach	0 (0)	0 (0)	0 (0)	0 (0)		
Valve type (n), %						
Edwards SAPIEN-XT	472 (83.8)	355 (82.8)	167 (81.5)	46 (78.0)		
Edwards SAPIEN3	52 (9.2)	39 (9.1)	15 (7.3)	6 (10.2)	0.50	0.53
Medtronic CoreValve	39 (6.9)	35 (8.2)	23 (11.2)	7 (11.9)		
Procedural complications (n), %						
Acute coronary obstruction	3 (0.5)	6 (1.4)	1 (0.5)	0 (0)	0.36	0.33
Disabling stroke	8 (1.5)	8 (1.9)	3 (1.5)	0 (0)	0.74	0.55
Acute kidney injury	37 (6.6)	29 (6.8)	24 (11.7)	9 (15.3)	0.014	0.025
Major vascular complication	25 (4.4)	20 (4.7)	13 (6.3)	3 (5.1)	0.75	0.76
Minor vascular complication	31 (5.5)	19 (4.4)	13 (6.3)	4 (6.8)	0.71	0.71
Life threatening/disabling bleeding	20 (3.6)	17 (4.0)	20 (9.8)	5 (8.5)	0.002	0.005
Major bleeding	71 (12.6)	53 (12.4)	27 (13.2)	14 (23.7)	0.10	0.16
Minor bleeding	61 (10.8)	47 (11.0)	34 (16.6)	5 (8.5)	0.11	0.14
Cardiac tamponade	8 (1.4)	5 (1.2)	7 (3.4)	1 (1.7)	0.20	0.27
2 valve implantation	7 (1.2)	5 (1.2)	3 (1.5)	0 (0)	0.84	0.67
Surgical conversion	5 (0.9)	5 (1.2)	5 (2.4)	0 (0)	0.28	0.26
Post pacemaker implantation (n=1162)	49/527 (9.3)	28/394 (7.1)	14/189 (7.4)	2/52 (4.6)	0.38	0.31
Post AR none–trivial	349/556 (62.8)	253/426 (59.4)	128/203 (63.1)	41/59 (69.5)		
Post AR mild	204/556 (36.7)	169/426 (39.7)	72/203 (35.5)	17/59 (28.8)	0.61	0.61
Post AR moderate	3/556 (0.5)	3/426 (0.7)	3/203 (1.5)	1/59 (1.7)		
Post AR severe	0/556 (0)	1/426 (0.2)	0/203 (0)	0/59 (0)		
Clinical outcomes						
Hospital stay after procedure, d	12.5 (6.0–14.3)	12.5 (7.0–15.0)	15.0 (8.0–18.0)	25.1 (9.0–22.5)	<0.001	<0.001
Intensive care unit stay, d	2.1 (1.0–2.0)	2.3 (1.0–2.0)	2.4 (1.0–2.0)	6.2 (1.0–4.0)	0.022	0.12
30-d mortality, %	5 (0.9)	4 (0.9)	3 (1.5)	2 (3.4)	0.32	0.49

Values are numbers (%) or mean±SD. AR indicates aortic regurgitation.

(n=2) groups. The prescreening gait speed levels reflecting frailty were related to poorer prognosis; thus, risk stratification before the TAVR procedure is possible. In the current series, New York Heart Association III/IV, creatinine value, baseline hemoglobin decline, and the presence of liver disease were independently associated with an increased risk of midterm mortality after TAVR. The worse prognosis associated with these factors have been confirmed in past TAVR investigations.[19–21] Moreover, the traditional surgical risk model using the STS score was found to be associated with increased mortality after TAVR; however, the relationship was diminished in the multivariable model. The surgical risk models for not only the STS score but also the logistic EuroSCORE are well known to predict a worse prognosis after an invasive therapy.[10,11,19–21]

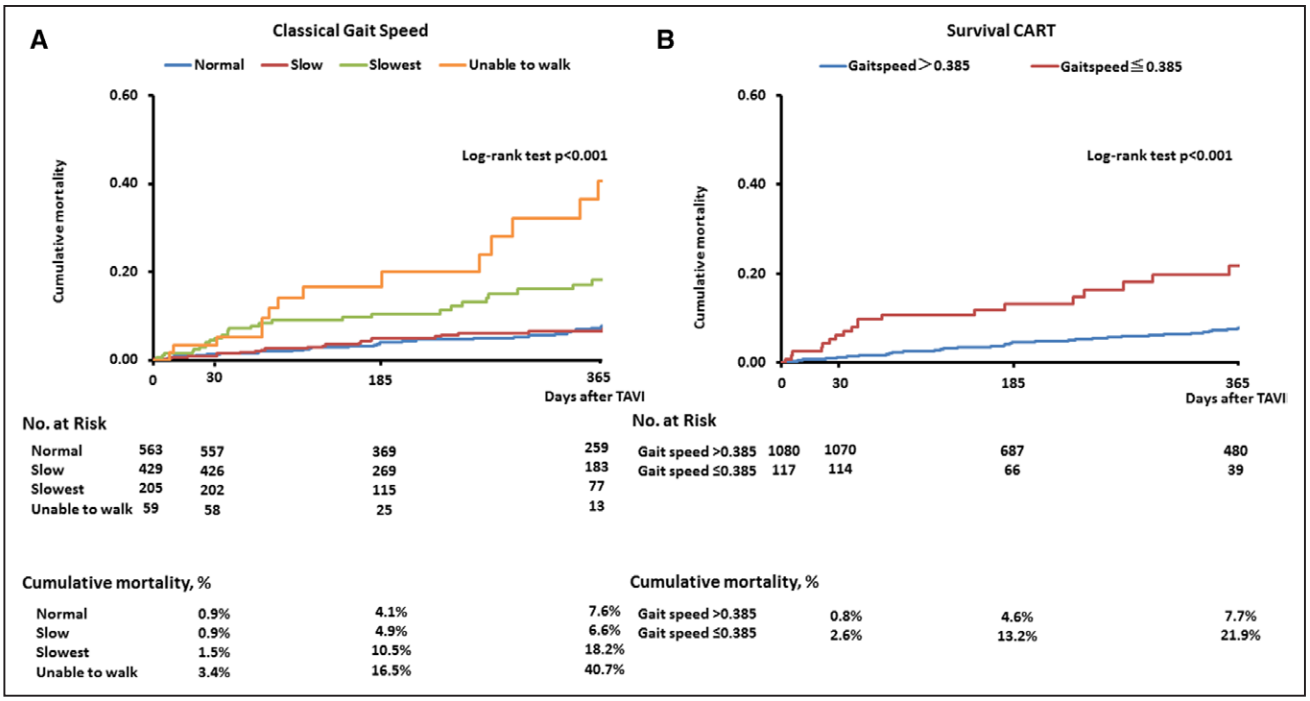

Figure 2. Kaplan–Meier curves showing cumulative all-cause mortality in the subgroups of classical gait speed (**A**) and survival CART (classification and regression tree; **B**) analysis.

When the patients were divided into transfemoral and non-transfemoral subgroups regardless of ambulatory level, baseline gait speed classification was still useful in the stratification of clinical outcomes. In addition, gait speed was significantly correlated with other frailty components, such as grip strength (muscle function), albumin level (nutritional status), MMSE score (cognitive function), and CFS score (semiquantitative frailty assessment). No definitive single tool for assessing the degree of frailty exists because frailty consists of several phenotypes within an individual. Nevertheless, gait speed may be considered as one of the main frailty markers, reflecting other frailty components. Assessing the gait speed as a reflection of frailty is useful and informative to operators for stratifying the subsequent risk of patients undergoing TAVR. Gait speed has

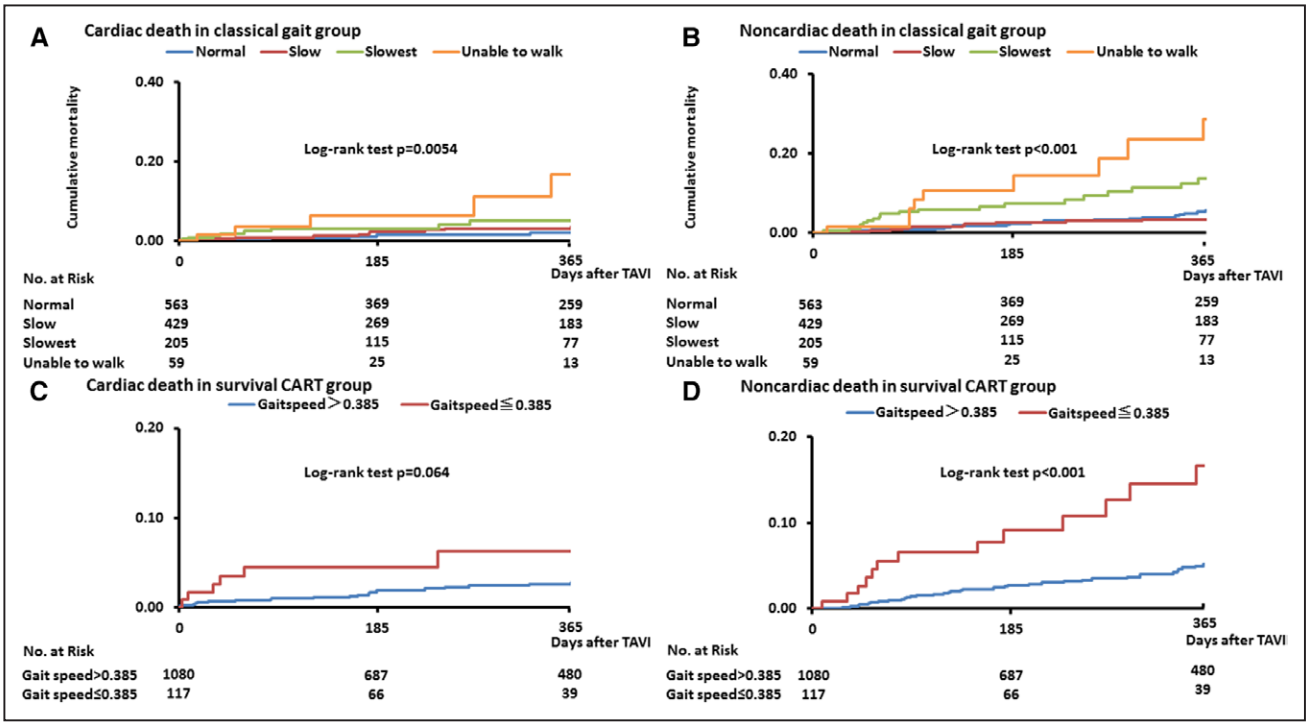

Figure 3. Kaplan–Meier curves showing cumulative cardiovascular and noncardiovascular mortality in the subgroups of classical gait speed and survival CART (classification and regression tree) analysis.

Table 3. Cox Regression Analysis for the Association Between Gait Speed Class and Clinical Outcomes

	Univariable Analysis			Multivariable Analysis					
				Model 1			Model 2		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Classical definition of gait speed									
Gait speed, normal (reference)									
Slow gait speed	1.06	0.96–1.02	0.82	1.08	0.66–1.75	0.77			
Slowest gait speed	2.15	1.33–3.47	0.002	2.01	1.20–3.38	0.008			
Unable to walk	5.03	2.78–9.11	<0.001	3.45	1.79–6.65	<0.001			
Survival CART analysis of gait speed									
Gait speed >0.385 m/sec (reference)									
Gait speed ≤0.385 m/sec	2.55	1.55–4.20	<0.001				2.40	1.43–4.05	0.001
Unable to walk	4.75	2.73–8.26	<0.001				3.21	1.75–5.88	<0.001
Adjusting factors									
Age (per 1 category increase)	1.00	0.96–1.03	0.79	0.97	0.94–1.00	0.060	0.97	0.94–1.00	0.061
Men (for women)	1.25	0.85–1.84	0.25	1.56	1.03–2.39	0.038	1.55	1.02–2.34	0.040
BSA (per 1.0 m^2 increase)	0.51	0.17–1.52	0.23	…			…		
STS score (per 1.0% increase)	1.04	1.03–1.06	<0.001	1.03	1.01–1.06	0.008	1.03	1.01–1.06	0.007
NYHA class III/IV (for I/II)	2.01	1.37–2.95	<0.001	1.64	1.09–2.47	0.018	1.64	1.09–2.47	0.018
BNP (per 1.0 pg/mL increase)	1.00	1.00–1.00	0.039	1.00	1.00–1.00	0.98	1.00	1.00–1.00	1.00
Creatinine (per 1.0 mg/dL increase)	1.74	1.41–2.13	<0.001	1.31	1.00–1.70	0.047	1.28	0.98–1.67	0.067
Hemoglobin (per 1.0 g/dL increase)	0.76	0.68–0.86	<0.001	0.82	0.73–0.93	0.002	0.81	0.72–0.92	0.001
Peripheral artery disease	2.28	1.53–3.39	<0.001	1.37	0.87–2.15	0.18	1.38	0.88–2.17	0.17
Prior MI	1.29	0.71–2.34	0.41	…			…		
Prior PCI	1.04	0.70–1.55	0.83	…			…		
Prior CABG	1.33	0.98–1.82	0.067	…			…		
Prior stroke	1.45	0.92–2.29	0.11	…			…		
Diabetes mellitus	1.41	0.96–2.06	0.082	…			…		
Hypertension	1.14	0.72–1.80	0.58	…			…		
Pulmonary disease	1.33	0.90–1.95	0.16	…			…		
Liver disease	2.70	1.32–5.55	0.007	2.05	0.92–4.55	0.080	1.98	0.89–4.43	0.096
Active cancer	1.35	0.77–2.36	0.29	…			…		
LVEF (per 1.0% increase)	1.01	0.99–1.02	0.47	…			…		
Transfemoral (for nontransfemoral)	0.53	0.36–0.77	0.001	0.66	0.43–1.02	0.059	0.67	0.43–1.03	0.067

BNP indicates B-type natriuretic peptide; BSA, body surface area; CABG, coronary artery bypass graft; CART, classification and regression tree; CI, confidence interval; HR, hazard ratio; LVEF, left ventricle ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and STS, society of thoracic surgeons predictive risk of mortality.

been generally considered as one of the important components in the evaluation of frailty.[7] Although there are several tools for the identification of frailty status in individual patients, gait speed is a simple tool for potentially predicting prognosis that does not require a geriatric specialist. A gait speed of <0.83 m/sec in patients undergoing conventional cardiac surgery has been validated to predict worse clinical outcomes.[10,11] In contrast, our data demonstrated an incremental increased mortality risk in the slowest group (gait speed <0.5 m/sec), whereas patients with a slow gait speed (0.5 to 0.83 m/sec) did not show an increased risk of mortality compared with that for patients with a normal gait speed. Survival CART analysis also indicated strict cutoff value of gait speed as 0.385 m/sec for predicting the worse prognosis after TAVR. The cutoff value of gait speed was calculated as 0.385 m/sec in a survival CART. Consistent with this, a Cox model with a spline curve of gait speed in relation to survival demonstrated a turning point for a significantly worse prognosis between 0.3 and 0.4 m/sec. The differential threshold in gait speed might be explained by differences in the conventional cardiac surgery and TAVR cohorts. A greater proportion of patients in the present TAVI cohort were categorized into the impaired gait speed groups (<0.83

Table 4. Cox Regression Analysis for the Association Between Gait Speed Class Excluded Unable to Walk and Clinical Outcomes

	Univariable Analysis			Multivariable Analysis					
				Model 1			Model 2		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Classical definition of gait speed									
Gait speed, normal (reference)									
Slow gait speed	1.06	0.66–1.68	0.82	1.04	0.64–1.71	0.86			
Slowest gait speed	2.14	1.32–3.46	0.002	1.84	1.07–3.15	0.027			
Survival CART analysis									
Gait speed >0.385 m/sec	2.55	1.54–4.20	<0.001				2.44	1.42–4.20	0.001
Adjusting factors									
Age (per 1 category increase)	0.99	0.95–1.02	0.48	0.97	0.93–1.00	0.084	0.97	0.93–1.00	0.071
Men (for women)	1.34	0.89–2.01	0.16	1.52	0.96–2.41	0.073	1.54	0.98–2.43	0.060
BSA (per 1 m^2 increase)	0.58	0.18–1.87	0.36	…			…		
STS score (per 1.0% increase)	1.03	1.01–1.06	0.002	1.02	0.99–1.06	0.20	1.02	1.00–1.06	0.16
NYHA class III/IV (for I/II)	2.13	1.41–3.22	<0.001	1.75	1.12–2.72	0.014	1.72	1.11–2.68	0.015
BNP (per 1.0 pg/mL increase)	1.00	1.00–1.00	0.48	1.00	1.00–1.00	0.48	1.00	1.00–1.00	0.49
Creatinine (per 1.0 mg/dL increase)	1.77	1.43–2.19	<0.001	1.37	1.02–1.85	0.038	1.34	1.00–1.81	0.057
Hemoglobin (per 1.0 g/dL increase)	0.79	0.70–0.90	<0.001	0.82	0.72–0.94	0.004	0.82	0.71–0.93	0.003
Peripheral artery disease	2.21	1.43–3.40	<0.001	1.47	0.89–2.45	0.13	1.48	0.89–2.46	0.13
Prior MI	1.37	0.73–2.57	0.32	…			…		
Prior PCI	1.01	0.66–1.55	0.96	…			…		
Prior CABG	1.32	0.95–1.84	0.097	…			…		
Prior stroke	1.40	0.85–2.30	0.19	…			…		
Diabetes mellitus	1.42	0.94–2.14	0.092	…			…		
Hypertension	1.34	0.80–2.26	0.27	…			…		
Pulmonary disease	1.18	0.77–1.81	0.44	…			…		
Liver disease	2.69	1.24–5.80	0.012	1.65	0.64–4.24	0.30	1.58	0.61–4.09	0.35
Active cancer	1.24	0.66–2.33	0.51	…			…		
LVEF (per 1.0% increase)	1.00	0.98–1.02	0.83	…			…		
Transfemoral (for nontransfemoral)	0.53	0.35–0.80	0.003	0.63	0.39–1.02	0.059	0.64	0.39–1.03	0.063

BNP indicates B-type natriuretic peptide; BSA, body surface area; CABG, coronary artery bypass graft; CART, classification and regression tree; CI, confidence interval; HR, hazard ratio; LVEF, left ventricle ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and STS, society of thoracic surgeons predictive risk of mortality.

m/sec). The importance of subgrouping based on gait speed, especially in TAVR cohorts, has been demonstrated in previous investigations.[15,16] Moreover, a previous report indicated that the optimal marker of frailty in terms of gait speed was a gait speed of <0.57 m/sec, which is close to gait speed <0.5 m/sec and our results of survival CART.[16] Although our cutoff value for gait speed was similar to those in previous investigations, potential ethnic differences should be considered. The results highlight the importance of grip strength assessment before TAVR. However, the current cutoff value of gait speed should not be overstated in generalizing the present results. The present study also demonstrated that patients defined as unable to walk were at an elevated risk of mortality after TAVR compared with that for patients with a normal gait speed. However, the cohort of patients unable to walk was difficult to examine precisely because of the complex patient backgrounds and differing reasons for the inability to walk. Patients with heart failure—a nonelective situation—and severely distressed clinical symptoms were excluded from the present analysis. Although the accuracy for the unable-to-walk group is debatable, the cumulative 1-year mortality rates of 40.7% were considerably higher than that for the other groups. Overall, the above findings highlight the importance of making decisions based on a careful analysis of the risk–benefit balance before performing the TAVR procedure in patients with a lower gait speed <0.5 m/sec, ≤0.385 m/sec, or unable to walk. Gait speed assessment has potential in identifying patients at risk for mortality after TAVR, which would help refine patient selection and further characterize the concept of futility in TAVR candidates. Operators should reduce the perioperative complications and

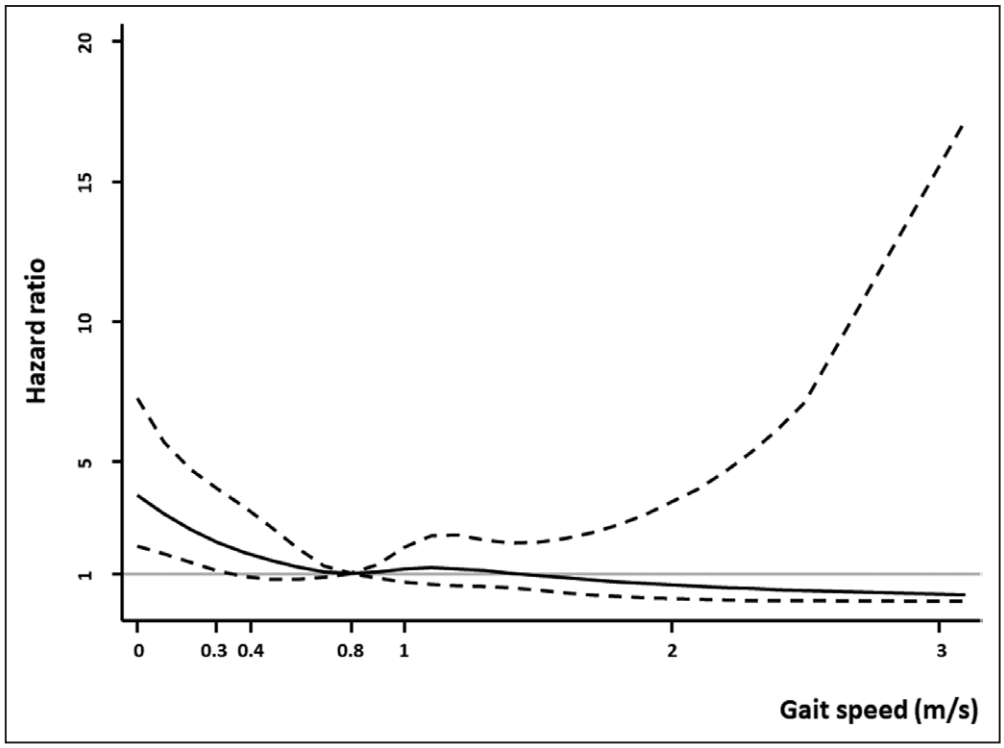

Figure 4. A continuous relationship between gait speed and hazard ratio for mortality according to a restricted cubic spline. The reference value of gait speed was set at 0.83 m/s. Solid and dotted lines represent the hazard ratio and its 95% confidence interval, respectively.

continue optimal postoperative care in such extremely frail patients undergoing TAVR.

Study Limitations

The present study has several limitations to address. Although the present study was based on Japanese multicenter registry data, which consists of a relatively large number of patients, only 48 patients were in the unable-to-walk group, reducing power for the assessment of prognosis. Although a recent national USA study revealed a significant relationship between gait speed and 30-day outcome in patients who underwent TAVR,[10] the current study found no significant differences among the 4 groups. This result might be explained by a relatively small study population or race-related differences. In addition, the excellent overall 30-day mortality rate in the current study (1.9%) may have created difficulty in finding statistical differences among the 4 groups. Another issue concerns the baseline clinical characteristics, which differed among the 4 groups. Although these differences were adjusted for in the Cox regression multivariable models, other potential confounding factors might have not been corrected. Moreover, a minor differential length in the evaluation of gait speed existed, with 2 centers using a 15-feet walking test (4.57 m) and the other 12 centers using a 5-m walking test; however, there were no significant differences in gait speed between the centers (data not shown). The evaluations of gait speed were dependent on the center protocol, as in other clinical investigations. Although data on serial changes in gait speed after TAVR might be informative, this registry lacked information on procedural changes in gait speed. The relatively longer hospital stay in the present study, in comparison with previous investigations, reflects the local Japanese practice and early experience of the TAVR procedure. Thus, the relationship between the length of the hospital stay and clinical outcomes remains uncertain. Further investigations are required to clarify the impact of the length of the hospital stay on clinical outcomes.

Conclusions

The present study revealed an increased midterm mortality rate after TAVI in patients with a gait speed of 0.385~0.5 m/sec, or unable to walk as compared with that for patients with a normal gait speed. These findings were not attenuated after adjusting for confounders. Therefore, in addition to considering the traditional surgical risk models, such as the EuroSCORE and STS score, prescreening for gait speed levels reflecting frailty may aid in risk stratification before the TAVI procedure.

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Disclosures

Drs Yamamoto, Koyama, Tada, Naganuma, Araki, Shirai, Tabata, Watanabe, and Hayashida are clinical proctors for Edwards Lifesciences. Drs Yamamoto, Naganuma, and Watanabe are clinical proctors for Medtronic.

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Gait Speed Can Predict Advanced Clinical Outcomes in Patients Who Undergo Transcatheter Aortic Valve Replacement: Insights From a Japanese Multicenter Registry

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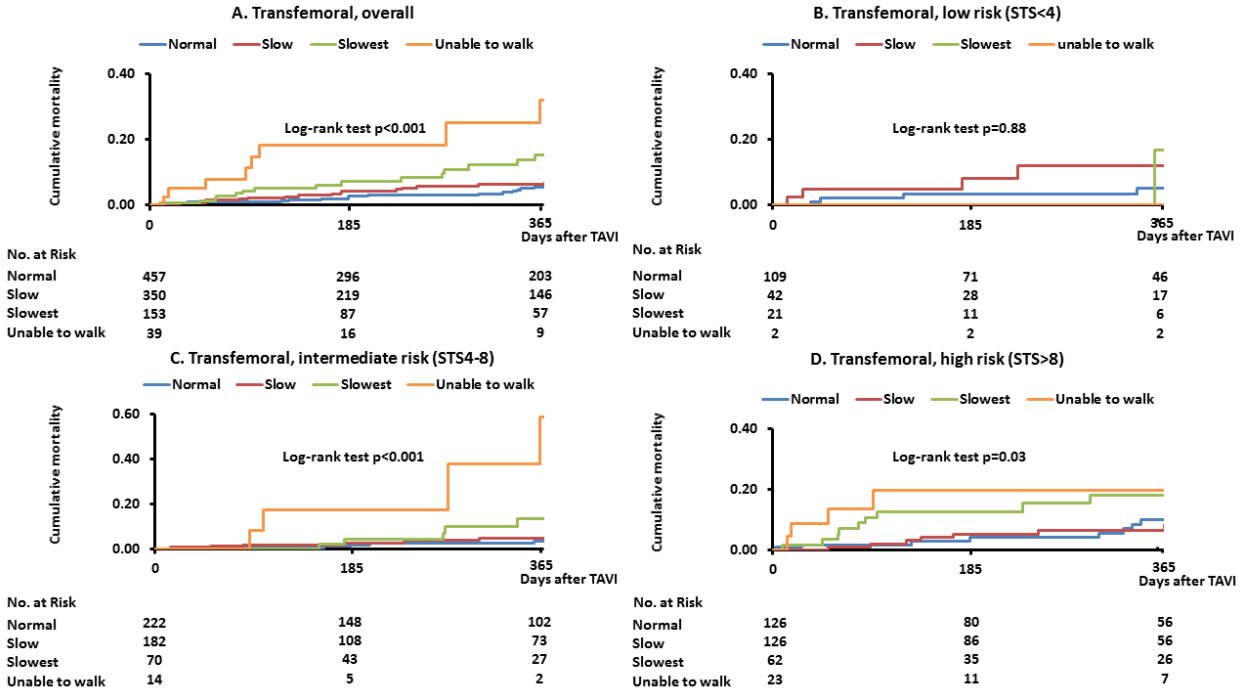
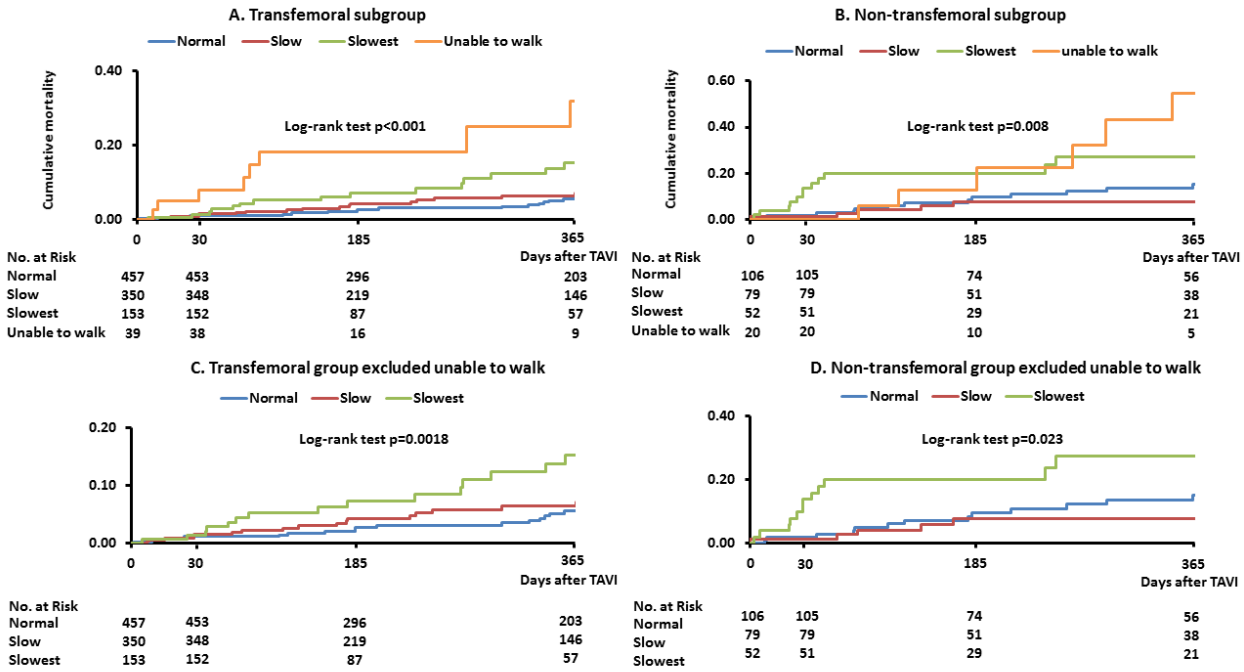
SUPPLIMENTAL MATERIAL



Supplemental Figure 1 Kaplan–Meier curves showing cumulative mortality in the subgroups of transfemoral, transfemoral low risk (STS <4), transfemoral intermediate risk (STS 4-8) and transfemoral high risk (STS >8).

STS: Society of Thoracic Surgeons Predictive Risk of Mortality



Supplemental Figure 2 Kaplan–Meier curves showing cumulative mortality in the subgroups of transfemoral and non-transfemoral (A-B). Kaplan–Meier curves showing cumulative mortality in the subgroups of transfemoral and non-transfemoral excluding those unable to walk (C-D).