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ORIGINAL RESEARCH

Identification of Frailty Using a Claims-Based Frailty Index in the CoreValve Studies: Findings from the EXTEND-FRAILTY Study

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BACKGROUND: In aortic valve disease, the relationship between claims-based frailty indices (CFIs) and validated measures of frailty constructed from in-person assessments is unclear but may be relevant for retrospective ascertainment of frailty status when otherwise unmeasured.

METHODS AND RESULTS: We linked adults aged ≥65 years in the US CoreValve Studies (linkage rate, 67%; mean age, 82.7±6.2 years, 43.1% women), to Medicare inpatient claims, 2011 to 2015. The Johns Hopkins CFI, validated on the basis of the Fried index, was generated for each study participant, and the association between CFI tertile and trial outcomes was evaluated as part of the EXTEND-FRAILTY substudy. Among 2357 participants (64.9% frail), higher CFI tertile was associated with greater impairments in nutrition, disability, cognition, and self-rated health. The primary outcome of all-cause mortality at 1 year occurred in 19.3%, 23.1%, and 31.3% of those in tertiles 1 to 3, respectively (tertile 2 versus 1: hazard ratio, 1.22; 95% CI, 0.98–1.51; P=0.07; tertile 3 versus 1: hazard ratio, 1.73; 95% CI, 1.41–2.12; P<0.001). Secondary outcomes (bleeding, major adverse cardiovascular and cerebrovascular events, and hospitalization) were more frequent with increasing CFI tertile and persisted despite adjustment for age, sex, New York Heart Association class, and Society of Thoracic Surgeons risk score.

CONCLUSIONS: In linked Medicare and CoreValve study data, a CFI based on the Fried index consistently identified individuals with worse impairments in frailty, disability, cognitive dysfunction, and nutrition and a higher risk of death, hospitalization, bleeding, and major adverse cardiovascular and cerebrovascular events, independent of age and risk category. While not a surrogate for validated metrics of frailty using in-person assessments, use of this CFI to ascertain frailty status among patients with aortic valve disease may be valid and prognostically relevant information when otherwise not measured.

Key Words: aortic valve disease ■ claims ■ frailty ■ SAVR ■ TAVR

Frailty, defined as "a state of increased vulnerability and reduced ability to maintain homeostasis after a stressful event resulting from impairment in multiple physiologic systems," is an important and often unmeasured risk factor for adverse outcomes among individuals undergoing aortic valve replacement (AVR) for severe aortic valve disease.[1,2] While multiple scales exist to measure frailty, they may be broadly categorized into 2 main types: a deficit-based frailty index (Rockwood index) that conceptualizes frailty as an accumulation of deficits over time[3] and a phenotype-based frailty index (Fried index) that conceptualizes frailty as a biologic syndrome.[2] This latter construct conceptualizes frailty as a biologic phenotype consisting of impairments across 5 domains: shrinking (ie, weight loss), exhaustion, weakness, slowness, and

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CLINICAL PERSPECTIVE

What Is New?

- In this study using US CoreValve Pivotal Studies data linked to Medicare claims, a claims-based frailty index based on the Fried index, identified individuals with worse impairments in frailty, disability, cognitive dysfunction, and nutrition and a higher risk of death, hospitalization, bleeding, and major adverse cardiovascular and cerebrovascular events, independent of age and risk category.

What Are the Clinical Implications?

- While well-validated quantitative metrics based on in-person assessments represent the gold-standard for frailty assessment, this claims-based frailty index represents an alternative for retrospective ascertainment of frailty status when otherwise unmeasured.

Nonstandard Abbreviations and Acronyms

AVR	aortic valve replacement
CAS	continued access study
CFI	claims-based frailty index
HiR	CoreValve high risk trial
MACCE	major adverse cardiovascular and cerebrovascular event
SAVR	surgical aortic valve replacement
SURTAVI	surgical or transcatheter aortic-valve replacement in intermediate-risk patients trial
TAVR	transcatheter aortic valve replacement

low physical activity.[2] By this latter definition, frailty is present in up to 63% of those undergoing transcatheter aortic valve replacement (TAVR) and is associated with a nearly 4-fold increased risk of death 1 year after TAVR[2,4,5] as well as functional decline at 6 months[6] and may be incrementally predictive of adverse risk beyond age and comorbidities alone.[7,8]

At the same time, frailty is often unmeasured in clinical trials and is not captured by traditional risk scores used to risk stratify individuals for AVR.[9] Moreover, in contrast to well-defined and validated frailty metrics using in-person measurements, physicians' subjective assessments of frailty may not significantly predict risk in TAVR.[9] As such, retrospective ascertainment of frailty status, using claims algorithms developed on the basis of such validated metrics of frailty, has been advocated to improve risk prediction,[10] assessment of hospital care quality,[11] and evaluation of study generalizability[12] when frailty assessment using these validated techniques has not been performed. While we have previously demonstrated that a claims-based frailty index (CFI) identifies individuals undergoing TAVR at higher risk of adverse outcomes than comorbidities alone using nationwide claims data,[10] whether it identifies individuals with a greater burden of frailty-related health deficits and similarly identifies an increased risk of adverse outcomes in a clinical trial population remains uncertain. Although not intended to replace previously validated techniques to assess frailty using in-person measurement, it is possible that CFIs could have a role in retrospectively ascertaining one's frailty status in data sets where this key risk marker is not otherwise measured (Figure 1).

As such, in the US CoreValve studies, we evaluated the concordance between health deficits related to frailty, measured using rigorous trial assessments, and a single CFI measure, validated against the Fried definition of frailty,[13,14] to assess whether claims can validly identify individuals with a greater number of frailty-related deficits and predict the occurrence of adverse outcomes in this setting.

METHODS

Data Availability

As per prior data use agreements with Centers for Medicare and Medicaid Services and Medtronic, the data supporting the current study are not publicly available for review.

Study Population

As part of the National Heart, Lung, and Blood Institute–sponsored (1R01HL136708) EXTEND (Extending Trial-Based Evaluations of Medical Therapies Using Novel Sources of Data) study, we previously linked Medicare inpatient claims to the US CoreValve Pivotal Trials data set. We subsequently examined the relationship of a single CFI and baseline covariates and outcomes in the US CoreValve Pivotal Trial data set as part of the EXTEND-FRAILTY substudy. This data set consists of a set of trials comparing TAVR using the self-expanding Medtronic CoreValve bioprosthesis with surgical AVR (SAVR). Details on this linkage have been published previously.[12] Data from patients included in the US CoreValve HiR (High Risk trial), SURTAVI (Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients)

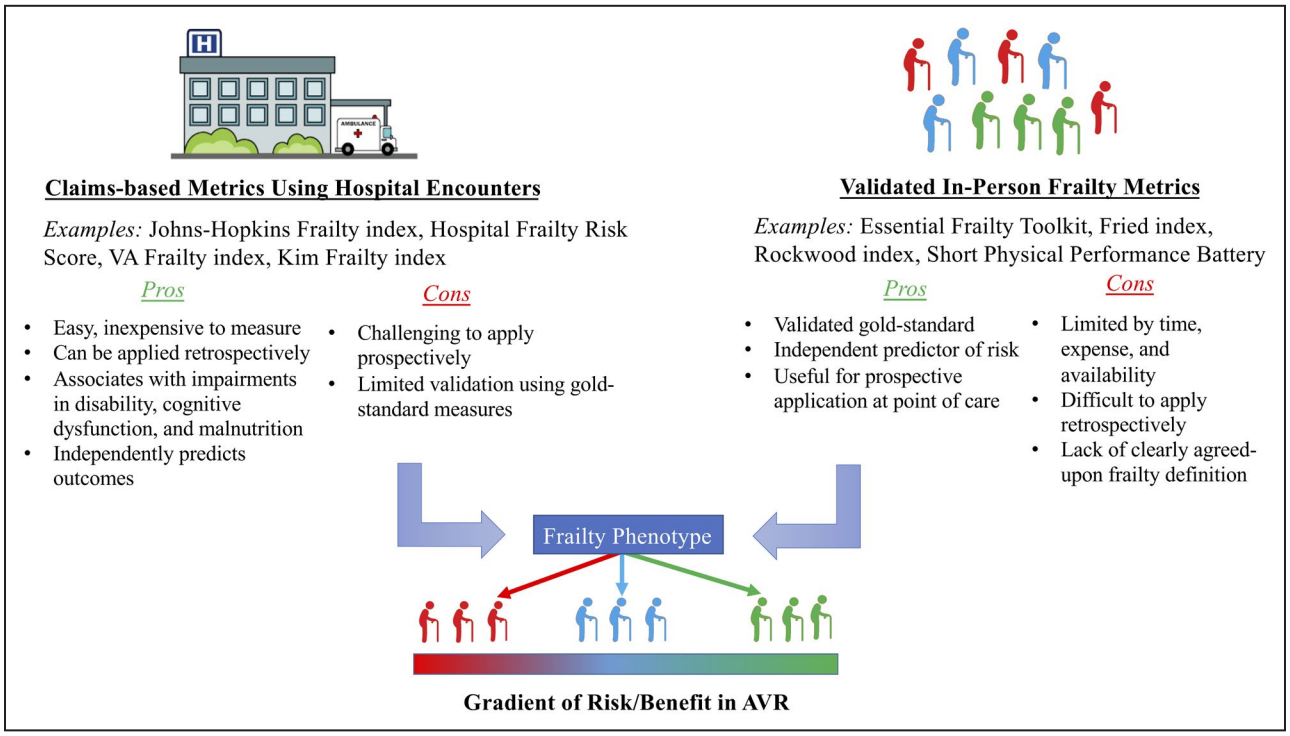

Figure 1. Schematic depicting relative advantages and disadvantages of methods to ascertain frailty in patients with severe aortic stenosis being evaluated for aortic valve replacement.
Schematic depicting the role of different data sources, namely, administrative claims and validated in-person metrics for evaluation of the frailty phenotype. Claims-based frailty indices are easy and inexpensive to measure and can be applied retrospectively but few have been validated against gold-standard definitions for frailty. Conversely, validated metrics of frailty using in-person measures may be useful prospectively to assess an individual's frailty status but may be limited by time, expense, and availability and are challenging to apply retrospectively. AVR indicates aortic valve replacement and VA, Veteran's Affairs.

trial, and single-arm CAS (Continued Access Study) who could be successfully linked to US Centers for Medicare and Medicaid Services Medicare Provider Analysis and Review data set with procedure dates February 2, 2011, to September 30, 2015, were included. The CoreValve HiR randomized individuals at high surgical risk with severe aortic stenosis to undergo TAVR with the Medtronic CoreValve bioprosthesis versus SAVR.[15] The SURTAVI trial randomized individuals at intermediate surgical risk with severe aortic stenosis to undergo TAVR with the Medtronic CoreValve bioprosthesis versus SAVR.[16] The CAS represents a single-arm cohort study of both extreme risk and high risk US TAVR recipients included in the US CoreValve trials intended for follow-up of outcomes and adverse events.[12] Only high-risk CAS patients were included in this analysis. These particular studies were chosen on the basis of the high prevalence of frail individuals and overlap with the use of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) claims before October 1, 2015.

The Medicare Provider Analysis and Review database used consists of a 100% sample of inpatient discharge claims (Part A) for Medicare Fee-for-Service beneficiaries and has been used extensively for health services research. As direct patient identifiers were not available in the US CoreValve Pivotal Trials data set, we previously linked the Medicare Provider Analysis and Review and trial data sets using a deterministic matching strategy based on age, date of birth, sex, procedure dates, admission and discharge dates, and hospital identification.[12] Patients aged <65 years or those undergoing AVR at a Veterans Affairs or European hospital were excluded.

Of those initially included in the US CoreValve HiR (N=750), SURTAVI (N=1660), or the high-risk group of the CAS (N=1108), 2520 (71.6%) were able to be successfully linked including 600 (80%) individuals in the US CoreValve HiR, 1005 (60.5%) individuals in SURTAVI, and 915 (82.6%) individuals in the CAS (Figure 2). Of those in the US CoreValve HiR, 15 individuals (2.0%) were excluded because they were aged <65 years or had an index procedure at a Veterans Affairs or European hospital. Of those in SURTAVI, 355 individuals (21.4%) were excluded because they were aged <65 years or had an index procedure at a Veterans Affairs or European hospital. Of those in the

High Risk CAS, 34 individuals (3.1%) were excluded because they were aged <65 or had an index procedure at a Veterans Affairs or European hospital. As Medicare Advantage health maintenance organizations represented 13% to 30% of Medicare enrollees during the time period, the majority of nonmatched individuals were likely enrolled in Medicare Advantage, for which claims data were not available. As the SURTAVI trial enrolled a younger and more international cohort, rates of linkage were lower. Subsequently, 163 individuals (9.8%) in SURTAVI were excluded because of procedure dates after October 1, 2015, the date when *International Classification of Diseases, Tenth Revision* was introduced in the United States. The study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center with a waiver of informed consent.

Covariates

Clinical and comorbidity data were determined for individuals undergoing AVR using baseline variables as defined and recorded in the trial data sets, broadly categorized into demographics, comorbidities, risk scores, and procedural variables (Table S1).

Frailty-Related Health Deficits

Well-understood health deficits, related to frailty or disability status and measured during trial baseline assessment, were broadly categorized into domains of functional status assessment, severity of lung disease, nutrition, weakness/slowness, cognitive dysfunction, and disability (Table S2).

Functional status was defined using baseline symptom questionnaires. Individuals in the CoreValve trials

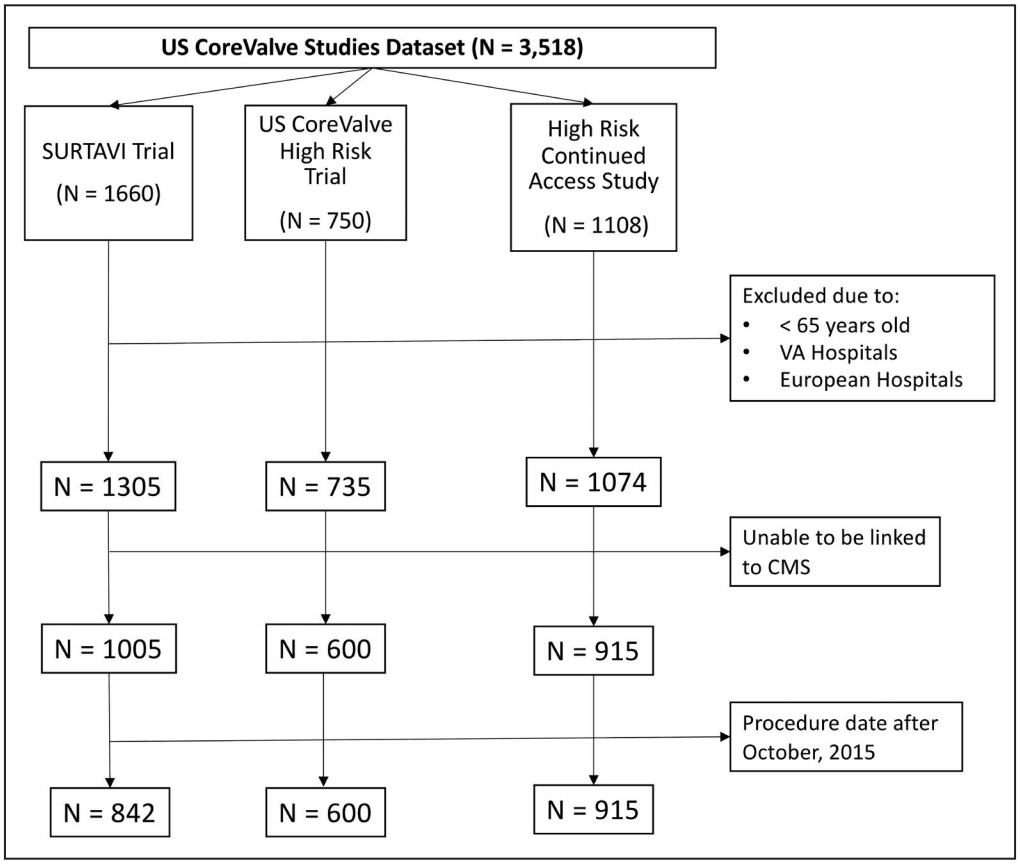

Figure 2. Study schematic displaying results of study linkage.
Linkage strategy used in the current study. Of 750 individuals in the US CoreValve High Risk Trial, 15 were excluded because they were aged <65 years or undergoing aortic valve replacement at a Veterans Affairs or European hospital. Of the 735 remaining, 135 were unable to linked to Medicare data. Of the 1108 individuals in the High Risk Continued Access Study (CAS), 34 were excluded because they were aged <65 years old or undergoing aortic valve replacement at a Veterans Affairs or European hospital. Of the 1074 remaining, 159 were unable to linked to Medicare data. Of the 1660 individuals in the SURTAVI trial, 355 were excluded because they were aged <65 years old or undergoing aortic valve replacement at a Veterans Affairs or European hospital. Of the 1305 remaining, 200 were unable to be linked to Medicare data. Subsequently, 163 were excluded because of procedure dates after October 1, 2015. CMS indicates Centers for Medicare and Medicaid Services; VA, Veterans Affairs; and SURTAVI, Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients Trial.

underwent baseline assessment of the Kansas City Cardiomyopathy Questionnaire, the 5-level EQ-5D questionnaire, the 12-item Short Form Survey, and the 36-item Short Form Survey (SF-36; SURTAVI only).[17–20] The Kansas City Cardiomyopathy Questionnaire is a 23-item questionnaire, graded from 0 to 100 with higher scores reflecting better health status, with 2 summary scores for overall functioning (overall summary score) and symptom-specific functioning (clinical summary score).[17] The EQ-5D is a 5-item questionnaire assessing generic health status on 5 dimensions, those being mobility, self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression.[18] The 12-item Short Form Survey represents a 12-item questionnaire, graded from 0 to 100 with higher scores reflecting better health status, with 2 composite scores for physical and mental functioning.[19] Similarly, the SF-36 represents a 36-item questionnaire, graded from 0 to 100 with higher scores reflecting better health status, with 2 composite scores for physical and mental functioning.[20]

Outcomes

The primary outcome for this analysis was 1-year all-cause mortality. All outcomes were defined as per the original trial protocols (Table S3). Secondary outcomes included acute kidney injury, bleeding, all stroke or transient ischemic attack, aortic reintervention, hospitalization, myocardial infarction, and major adverse cardiovascular and cerebrovascular event (MACCE), defined as a composite of all-cause death, myocardial infarction, stroke, or aortic reintervention.

Ascertainment of Frailty Status

Frailty status was ascertained using claims via the Johns Hopkins CFI published by Segal et al.[13] This CFI was developed using *International Classification of Diseases, Ninth Revision, Clinical Modification* Medicare claims linked to data from the Cardiovascular Health Study and externally validated in the National Health and Aging Trend Study.[13,14] This CFI was developed and validated using claims chosen on the basis of their correlation with the Fried index as the reference standard, predicts outcomes similarly to the Fried index,[13] and has been used previously in studies of frailty.[21] While other CFIs have been developed previously, all other scales are based on the accumulation of deficits definition of frailty. A CFI based on the Fried conception was chosen so as to be more closely aligned with the conceptualization of frailty as a physical syndrome that can improve or worsen over time. Claims (Table S4) for hospitalizations in the 6 months preceding the baseline visit were used to construct the frailty index.[13] In addition to treating the index as a continuous variable, a previously proposed cutoff of >0.20 was used to define an individual's frailty status.[13]

Statistical Analysis

The distribution of the CFI in the sample was described using means and SDs and displayed graphically using a histogram. The number and proportion of the sample with frailty using a dichotomous cutoff of >0.20 was determined. We first divided the CFI into tertiles and compared baseline trial variables (described using means±SDs for continuous variables and frequencies and percentages for categorical variables) across tertiles using analysis of variance for continuous variables and chi-squared tests for categorical variables. Overall rather than study-specific tertiles were used throughout the analysis.

Subsequently, to evaluate the construct validity of the CFI, we compared frailty-related variables, collected during baseline trial assessments, across CFI tertiles using analysis of variance for continuous variables and chi-squared tests for categorical variables.

Next, rates of adverse outcomes at 1 year by CFI tertile were calculated using Kaplan-Meier estimates in both the combined data set and stratified by study group (eg, HiR, CAS, or SURTAVI). Kaplan-Meier curves and the log-rank test were used to compare the primary outcome of death across CFI tertiles. Cox proportional hazards models were used to model time to all nondeath outcomes by CFI tertile, accounting for the competing risk of death using Fine-Gray competing risk estimates.[22] Individuals without events were censored at 1 year after their procedure. Analyses were subsequently adjusted for age, sex, New York Heart Association class, and the Society of Thoracic Surgeons risk score to assess if results changed. All analyses were performed using SAS version 9.4 or JMP version 15.0 (SAS Institute, Cary, NC) using a 2-tailed P value <0.05 to define significance.

RESULTS

Overall Results

A total of 2357 (67.0%) of individuals in the CoreValve HiR, SURTAVI, and High Risk group of the CAS were able to be successfully linked to Medicare data and were included in the analysis (Figure 2). Individuals whose records could not be linked were overall similar to those who could be linked (Table S5), although the age, Society of Thoracic Surgeons risk score, and the proportion with heart failure were higher, and the Logistic EuroSCORE was lower in the linked group.

Of those included, the mean CFI score was 0.27±0.13 and the median (interquartile range) CFI was 0.25 (0.17–0.35) (Figure S1). The mean age was 82.7±6.2 years and 1015 (43.1%) were women. Overall, 1656 (70.3%) received TAVR and 701 (29.7%) received SAVR with femoral access in 1445 of those receiving TAVR (87.3%). Using a threshold cutoff of 0.20 to define

frailty, 1529 (64.9%) of the sample was considered frail. A total of 787 (33.3%) were in tertile 1 (CFI ≤0.20), 788 (33.4%) were in tertile 2 (CFI, 0.21–0.31) and 782 (33.2%) were in tertile 3 (CFI ≥0.32).

Comparison of Baseline Trial Characteristics Across CFI Tertiles

Use of TAVR was higher in the higher CFI tertiles (Table 1; tertile 3 versus 1: 74.7% versus 63.2%; *P*<0.001 across tertiles). Those in higher CFI tertiles were older (tertile 3 versus 1: mean age, 87.2±4.0 versus 77.4±5.6; *P*<0.001) and more frequently women (tertile 3 versus 1: 54.0% versus 32.8%; *P*<0.001). The number of comorbidities was similar across frailty tertiles (tertile 3 versus 1: mean Charlson comorbidity index, 5.0±2.3 versus 5.1±2.1; *P*=0.77) with nearly all individuals having a history of hypertension (tertile 3 versus 1: 92.7% versus 95.7%; *P*=0.03). Those in higher frailty tertiles more frequently had a history of heart failure (tertile 3 versus 1: 92.2% vs. 53.5%, *P*<0.001) but less frequently had insulin-dependent diabetes mellitus (tertile 3 versus 1: 8.7% versus 17.5%; *P*<0.001). Despite similar rates of prior percutaneous coronary intervention across tertiles (*P*=0.93), rates of coronary artery bypass grafting were lower among those in higher frailty tertiles (tertile 3 versus 1: 17.1% versus 36.7%; *P*<0.001). The Society of Thoracic Surgeons risk score was higher in those with a higher CFI (tertile 3 versus 1: 8.0±3.4 versus 5.4±2.5; *P*<0.001).

Comparison of Frailty-Related Health Deficits Across CFI Tertiles

Those in the higher CFI tertiles had a higher proportion of health deficits related to frailty and disability, across all domains except for severity of lung disease (Table 2). Specifically, those in the higher CFI tertiles had a greater proportion of individuals with impairments in nutrition including low serum albumin, unplanned weight loss (tertile 3 versus 1:, 9.7% versus 3.2%; *P*=0.04) and a lower body mass index (tertile 3 versus 1: 27.3±5.4 versus 30.2±6.4; *P*<0.01), despite no differences in anemia requiring transfusion (*P*=0.58). Those in higher CFI tertiles had greater impairments in weakness/slowness, with a greater proportion having falls within 6 months, 5-meter walk time <0.5 m/s, and a grip strength below threshold. Additionally, cognitive function as assessed by the Mini-Mental Status Exam was worse in higher CFI tertiles (tertile 3 versus 1: 26.3±2.8 versus 27.3±2.5; *P*<0.001). Those in higher CFI tertiles had increased disability with dependence in living, bathing, dressing, toileting, and transferring (all *P*<0.05), though no differences in urinary incontinence (*P*=0.11). Additionally, self-reported quality of life was worse in those in the high CFI tertiles with worsened Kansas City Cardiomyopathy Questionnaire overall and summary scores and EQ-5D (*P*<0.05 for all), despite no significant differences across tertiles in the 12-item Short Form Survey and SF-36 (*P*>0.05 for both).

Despite a lower forced expiratory volume in 1 second (*P*<0.001) in those with higher CFI tertiles, the proportion with severe lung disease (tertile 3 versus 1: 7.2% versus 12.2%; *P*<0.001) and requirement for home oxygen (tertile 3 versus 1: 7.9% versus 11.8%; *P*=0.006) was lower, and the diffusion capacity for carbon monoxide was higher (*P*=0.02).

Primary Outcome

At 1 year in the overall sample, 19.3% of those in tertile 1, 23.1% in tertile 2, and 31.3% of those in tertile 3 of the CFI had died (tertile 2 versus 1: hazard ratio [HR], 1.22; 95% CI, 0.98–1.51; *P*=0.07; tertile 3 versus 1: HR, 1.73; 95% CI, 1.41–2.12; *P*<0.001) (Figure 3). In the HiR trial, 33.1% of those in tertile 1, 31.1% in tertile 2, and 47.7% in tertile 3 died at 1 year (tertile 2 versus 1: HR, 0.91; 95% CI, 0.65–1.27; *P*=0.91; tertile 3 versus 1: HR, 1.57; 95% CI, 1.16–2.13; *P*=0.004) (Table S6). In the CAS study, 22.2% of those in tertile 1, 25.7% of those in tertile 2, and 26.2% of those in tertile 3 died at 1 year (tertile 2 versus 1: HR 1.16, 95% CI 0.81–1.67, *P*=0.41; tertile 3 versus 1: HR, 1.18; 95% CI, 0.84–1.66; *P*=0.35) (Table S7). In the SURTAVI study, 13.1% of those in tertile 1, 14.4% of those in tertile 2, and 17.0% of those in tertile 3 died at 1 year (tertile 2 versus 1: HR, 1.11; 95% CI, 0.75–1.65; *P*=0.59; tertile 3 versus 1: HR, 1.35; 95% CI, 0.84–2.16; *P*=0.22) (Table S8).

Secondary Outcomes

At 1 year in the overall sample (Table 3), 27.8% of those in tertile 1, 32.9% in tertile 2, and 36.7% of tertile 3 had experienced a MACCE event (tertile 2 versus 1: HR, 1.22; 95% CI, 1.03–1.45; *P*=0.03; tertile 3 versus 1: HR, 1.39; 95% CI, 1.18–1.65; *P*<0.001). Compared with those in tertile 1, those in tertile 2 (34.1% versus 27.3%; HR, 1.30; 95% CI, 1.10–1.55; *P*=0.002) and tertile 3 (42.2% versus 27.3%; HR, 1.68; 95% CI, 1.43–1.98; *P*<0.001) more frequently had bleeding. Compared with tertile 1, tertile 2 more frequently had hospitalizations (19.9% versus 15.8%; HR, 1.30; 95% CI, 1.03–1.63; *P*=0.03) but not tertile 3 (19.2% versus 15.8%; HR, 1.26; 95% CI, 1.00–1.59; *P*=0.052). Rates of acute kidney injury, stroke or transient ischemic attack, myocardial infarction, aortic reintervention, or other events were similar (*P*>0.05 for all). Considering CFI as a continuous predictor, results were similar (Table S9). These results were overall consistent across studies (Tables S6–S8). Among the subgroups who received TAVR (N=1656; Table S10) or SAVR (N=701), results were substantially unchanged (Table S11).

Table 1. Baseline Demographic, Procedural, Risk Score, and Comorbidity Characteristics of CoreValve Study Participants Across CFI Tertiles

Characteristic	Observations, N	Tertile 1 (n=787)	Tertile 2 (n=788)	Tertile 3 (n=782)	*P* value
Demographics					
Age, y	2357	77.4±5.6	83.7±4.4	87.2±4.0	<0.001
Female sex, n (%)	2357	258 (32.8)	335 (42.5)	422 (54.0)	<0.001
Risk scores					
Society of Thoracic Surgeons risk score	2357	5.4±2.5	6.5±2.8	8.0±3.4	<0.001
Logistic EuroSCORE	2355	14.2±11.2	17.7±12.4	19.3±12.3	<0.001
Charlson comorbidity index	1511	5.1±2.1	5.1±2.2	5.0±2.3	0.77
Comorbidities					
Diabetes mellitus, n (%)					
Total	1515	172 (21.9)	192 (24.4)	221 (28.3)	<0.001
Controlled by insulin	2357	138 (17.5)	78 (9.9)	68 (8.7)	<0.001
History of hypertension	2357	753 (95.7)	749 (95.1)	725 (92.7)	0.03
Peripheral vascular disease	2351	339 (43.1)	314 (39.8)	311 (39.8)	0.33
Prior stroke	2356	80 (10.2)	79 (10.0)	90 (11.5)	0.57
Connective tissue diseases	1513	<11	<11	14 (2.2)	0.53
Immunosuppressive therapy	2355	97 (12.3)	70 (8.9)	75 (9.6)	0.06
Prior transient ischemic attack	2356	71 (9.0)	89 (11.3)	78 (10.0)	0.32
Cirrhosis	2355	14 (1.8)	<11	<11	0.02
Cardiac risk factors, n (%)					
Coronary artery disease	2357	598 (76.0)	588 (74.6)	527 (67.4)	<0.001
Prior CABG	2357	289 (36.7)	231 (29.3)	134 (17.1)	<0.001
Prior PCI	2357	255 (32.4)	260 (33.0)	251 (32.1)	0.93
Pacemaker or implantable defibrillator	2357	116 (14.7)	139 (17.6)	151 (19.3)	0.051
Prior myocardial infarction	2357	193 (24.5)	174 (22.1)	158 (20.2)	0.12
Congestive heart failure	2357	421 (53.5)	601 (76.3)	721 (92.2)	<0.001
Atrial flutter or fibrillation	2357	270 (34.4)	300 (38.1)	322 (41.3)	0.02
Procedural variables					
Treatment assignment, n (%)					
TAVR	2357	497 (63.2)	575 (73.0)	584 (74.7)	<0.001
SAVR		290 (36.9)	213 (27.0)	198 (25.3)	
Presence of a calcified aorta, n (%)					
No calcification	2353	128 (17.5)	102 (12.9)	102 (13.0)	0.15
Mild calcification		392 (49.8)	405 (51.4)	371 (47.4)	
Moderate calcification		207 (26.3)	201 (25.5)	227 (29.0)	
Severe calcification		60 (7.6)	77 (9.8)	79 (10.1)	
Chest wall deformity, n (%)	2357	<11	<11	<11	0.95
Hostile mediastinum, n (%)	1511	22 (6.2)	<11	<11	<0.001
Arterial access site, n (%)					
Femoral	1655	433 (55.0)	500 (63.5)	512 (65.5)	0.64
Subclavian		21 (2.7)	17 (2.2)	19 (2.4)	
Aortic		39 (5.0)	50 (6.3)	46 (5.9)	
Other		<11	<11	<11	
Number of valves implanted	1656	1.1±0.2	1.1±0.2	1.0±0.2	0.84

Values are listed as means±standard deviations unless otherwise specified. Individuals in tertile 1 had a CFI ≤0.20, those in tertile 2 had a CFI of 0.21 to 0.31, and those in tertile 3 had a CFI ≥0.32. CABG indicates coronary artery bypass grafting; CFI, claims-based frailty index; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

Table 2. Frailty-Related Characteristics of CoreValve Study Participants Across CFI Tertiles

Characteristic	Observations, N	Tertile 1 (N=787)	Tertile 2 (N=788)	Tertile 3 (N=782)	*P* value
Nutrition					
Body mass index, kg/m^2	2357	30.2±6.4	28.2±5.4	27.3±5.4	<0.001
Anemia requiring transfusion, n (%)	1447	55 (16.1)	75 (15.5)	110 (17.7)	0.58
Albumin <3.3 g/dL, n (%)	1492	48 (6.1)	54 (6.9)	109 (13.9)	0.009
Unplanned weight loss, n (%)	1515	25 (3.2)	47 (6.0)	76 (9.7)	0.04
Weakness/Slowness					
Falls in the past 6 months, n (%)	2357	93 (11.8)	136 (17.3)	186 (23.8)	<0.001
5-meter gait speed, s	2163	7.5±3.6	8.6±4.8	10.0±7.7	<0.001
5-meter gait speed <0.5 m/s, n (%)	2163	106 (13.5)	182 (23.1)	245 (31.3)	<0.001
Grip strength below threshold, n (%)	2320	528 (67.1)	497 (63.1)	472 (60.4)	0.008
Cognitive dysfunction					
Mini-Mental Status Exam score	2287	27.3±2.5	27.1±2.4	26.3±2.8	<0.001
Disability					
Does not live independently, n (%)	2357	23 (2.9)	33 (4.2)	71 (9.1)	<0.001
Does not bathe independently, n (%)	2357	23 (2.9)	28 (3.6)	65 (8.3)	<0.001
Does not dress independently, n (%)	2357	18 (2.3)	20 (2.5)	41 (5.2)	0.002
Does not toilet independently, n (%)	2357	<11	<11	24 (3.1)	<0.001
Does not transfer independently, no (%)	2357	13 (1.7)	17 (2.2)	40 (5.1)	<0.001
Does not feed independently, n (%)	2357	<11	<11	<11	0.79
Urinary incontinence, n (%)	2357	14 (1.8)	21 (2.7)	27 (3.5)	0.11
Functional status assessment					
New York Heart Association class, n (%)					
Class II	2357	214 (27.2)	188 (23.9)	160 (20.5)	0.03
Class III		496 (63.0)	526 (66.8)	540 (69.1)	
Class IV		69 (8.8)	69 (8.8)	78 (10.0)	
KCCQ overall summary score	2177	66.0±27.0	58.1±25.5	52.1±24.1	<0.001
KCCQ clinical summary score	2177	67.4±25.2	60.4±24.1	55.2±23.5	<0.001
EQ-5D index score	2162	0.79±0.18	0.76±0.18	0.74±0.19	<0.001
SF-12 physical component summary score	1445	30.6±8.6	31.5±9.2	31.0±8.4	0.41
SF-12 mental component summary score	1445	47.5±11.5	48.1±12.4	48.7±11.6	0.29
SF-36 physical component summary score	814	36.9±9.9	35.7±9.5	35.2±9.2	0.10
SF-36 mental component summary score	814	50.6±11.5	49.4±11.7	49.2±11.6	0.29
Severity of lung disease					
Society of Thoracic Surgeons chronic lung severity, n (%)					
None	2356	401 (51.0)	479 (60.8)	486 (62.1)	<0.001
Mild		176 (22.4)	171 (21.7)	169 (21.6)	
Moderate		114 (14.5)	83 (10.5)	71 (9.1)	
Severe		96 (12.2)	54 (6.9)	56 (7.2)	
Requirement for home oxygen, n (%)	2356	93 (11.8)	59 (7.5)	62 (7.9)	0.006
Forced expiratory volume in 1 s (mL)	1058	1850.6±806.0	1741.5±823.0	1580.1±587.0	<0.001
Diffusion capacity for carbon monoxide (%)	341	60.0±21.5	68.6±22.7	64.5±21.9	0.02

Values are listed as means±standard deviations unless otherwise specified. Individuals in tertile 1 had a CFI ≤0.20, those in tertile 2 had a CFI of 0.21 to 0.31, and those in tertile 3 had a CFI ≥0.32. CFI indicates claims-based frailty index; KCCQ, Kansas City Cardiomyopathy Questionnaire; SF-12, 12-item short form questionnaire; and SF-36, 36-item short form questionnaire.

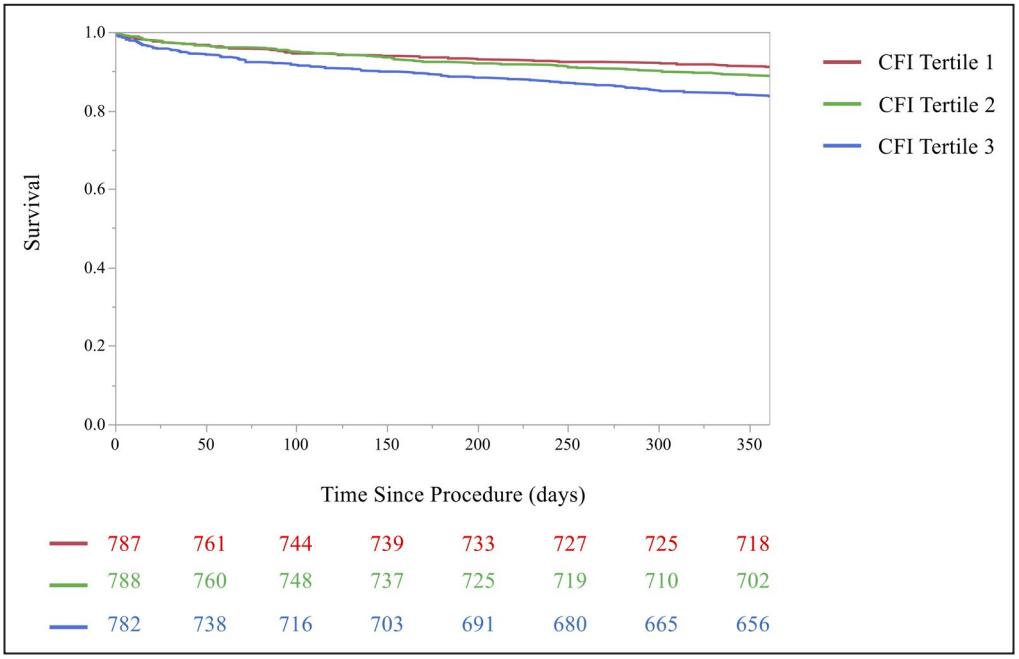

Figure 3. Kaplan-Meier curve demonstrating time to all-cause mortality by claims-based frailty index tertile.
Kaplan-Meier survival curve for all-cause mortality in the HiR and CAS studies according to time since aortic valve replacement. The red line indicates those in the CFI tertile 1 (CFI ≤ 0.20), the green line indicates those in CFI tertile 2 (CFI, 0.21–0.31), and the blue line indicates those in CFI tertile 3 (CFI ≥ 0.32). Numbers in the risk set at each time point are indicated below. CAS indicates US CoreValve Continued Access Study; CFI, claims-based frailty index and HiR, US CoreValve High Risk Study. Log-rank *P* value for the overall comparison <0.001.

Multivariable Analysis

After adjustment for age, sex, New York Heart Association class, and Society of Thoracic Surgeons score, those in CFI tertile 3 but not 2 continued to have an increased risk of death (tertile 3 versus 1; adjusted HR, 1.48; 95% CI, 1.12–1.96; *P*=0.006; tertile 2 versus 1: adjusted HR, 1.13; 95% CI, 0.88–1.45; *P*=0.33) (Table S12). Analyses of secondary end points also had similar results after adjustment for trial baseline variables (Table S12).

DISCUSSION

In this study of CoreValve HiR, SURTAVI, and CAS participants linked to Medicare claims, a CFI anchored to the Fried index demonstrated good construct validity in identifying individuals with health deficits related to frailty. Frailty was present in 64.9% of individuals. Nevertheless, higher CFI scores in this cohort identified individuals at higher risk of death, MACCE, hospitalization, and bleeding, despite adjustment for age, sex, and risk category. As a whole, these results suggest that, while well-validated techniques to assess frailty, using in-person measurements, remain the gold standard for assessing one's frailty status, use of the Johns Hopkins CFI has utility for retrospective ascertainment of one's frailty status in studies of aortic valve disease in circumstances where this important risk factor is unmeasured, and may capture relevant prognostic information over and above traditional risk scores.

Multiple CFIs exist for the evaluation of an individual's frailty status,[13,23–25] but only one, the Johns Hopkins CFI used in this study, is anchored to the Fried index.[13] This construct conceptualizes frailty as a biologic phenotype, associated but not synonymous with aging, consisting of impairments in 5 domains: shrinking (ie, weight loss), exhaustion, weakness, slowness, and low physical activity.[2] By contrast, other CFIs derive from the Rockwood cumulative-deficit conception of frailty that treats increasing frailty as an accumulation of deficits across multiple health domains.[26] The Johns Hopkins CFI was chosen for this study to be more closely aligned with the conceptualization of physical frailty as a syndrome that can improve or worsen over time. Moreover, though 1 prior CFI has been derived under the *International Classification of Diseases, Tenth Revision* framework based on clusters of resource usage, this CFI has only a modest correlation with tradition metrics of frailty including the Fried and Rockwood indices.[25] As such, it is unclear that this represents a true metric of frailty in the traditional conception, and further development of *International*

Table 3. Comparison of Outcomes by CFI Tertile in the Overall Cohort (N=2357)

Outcomes	Tertile 1 (N=787)	Tertile 2 (N=788)	Tertile 3 (N=782)	HR (95% CI) for Tertile 2 vs. 1	*P* value*	HR (95% CI) for Tertile 3 vs. 1	*P* value†
Death (N=579), n (%)	152 (19.3)	182 (23.1)	245 (31.3)	1.22 (0.98–1.51)	0.07	1.73 (1.41–2.12)	<0.001
MACCE (N=765), n (%)	219 (27.8)	259 (32.9)	287 (36.7)	1.22 (1.03–1.45)	0.03	1.39 (1.18–1.65)	<0.001
Acute kidney injury (N=277), n (%)	102 (13.0)	87 (11.0)	88 (11.3)	0.84 (0.63–1.11)	0.22	0.86 (0.65–1.14)	0.28
Bleeding (N=814), n (%)	215 (27.3)	269 (34.1)	330 (42.2)	1.30 (1.10–1.55)	0.002	1.68 (1.43–1.98)	<0.001
Stroke or transient ischemic attack (N=317), n (%)	100 (12.7)	108 (13.7)	109 (13.9)	1.09 (0.83–1.42)	0.54	1.11 (0.85–1.45)	0.45
Myocardial infarction (N=56), n (%)	18 (2.3)	22 (2.8)	16 (2.1)	1.23 (0.66–2.28)	0.52	0.90 (0.46–1.75)	0.75
Aortic reintervention (N=33), n (%)	15 (1.9)	12 (1.5)	<11	0.80 (0.37–1.70)	0.56	0.40 (0.16–1.04)	0.06
Hospitalization (N=431), n (%)	124 (15.8)	157 (19.9)	150 (19.2)	1.30 (1.03–1.63)	0.03	1.26 (1.00–1.59)	0.052
Other (N=74), n (%)	26 (3.3)	27 (3.4)	21 (2.7)	1.04 (0.61–1.77)	0.89	0.81 (0.46–1.44)	0.46

Percentages are determined using Kaplan-Meier estimates. Additionally, the hazard ratios and 95% CIs for the comparison of tertile 2 vs. 1 and tertile 3 vs. 1 are listed with the log-rank *P* values for these comparisons. For nondeath outcomes, estimates are adjusted for the competing risk of death using Fine-Gray subdistribution hazard models. Cell numbers <11 are suppressed from publication per Centers for Medicare and Medicaid Services policy. CFI indicates claims-based frailty index; HR, hazard ratio; and MACCE, major adverse cardiovascular and cerebrovascular events.

*Represents the *P* value for the comparison of CFI tertile 2 vs. tertile 1.

†Represents the *P* value for the comparison of CFI tertile 3 vs. tertile 1. Listed is the number and percentage of outcomes in each category occurring within 1 year from procedure by CFI tertile in the overall cohort.

Classification of Diseases, Tenth Revision–based frailty scales is needed.

The CFI used in the current study, which has been validated against the Fried definition of frailty as measured in the Cardiovascular Health Study, identified individuals at higher risk of death, MACCE, hospitalization, and bleeding in the CoreValve studies, despite adjustment for age, sex, New York Heart Association class, and Society of Thoracic Surgeons risk score, suggesting it may improve upon risk stratification using conventional risk metrics. Importantly, this increased risk of adverse outcomes was primarily (though not exclusively) observed among those in the highest CFI tertile, suggesting this increase in adverse risk may be most prominent in the frailest individuals.

In the current study, the Johns Hopkins CFI displayed good construct validity for identifying individuals with a higher burden of frailty-related health deficits in addition to worse outcomes. Importantly, the Johns Hopkins CFI identified individuals with greater impairments in disability (ie, impairment in activities of daily living/instrumental activities of daily living), cachexia/malnutrition, gait speed, and self-reported quality of life. Though the Fried index, which associates with this CFI, has been criticized for its lack of accounting for cognitive frailty,[27] the Johns Hopkins CFI nevertheless identified individuals with more cognitive dysfunction, suggesting that cognitive frailty may have significant overlap with other domains of frailty. Interestingly, the CFI was inversely related with severity of lung disease and not related to commonly used markers of frailty such as anemia or urinary incontinence. This finding may suggest that these markers represent poor surrogates for frailty in the older aged aortic stenosis population or that the Johns Hopkins CFI does not readily identify them. Nevertheless, despite this, the Johns Hopkins CFI was associated with significant prognostic utility. As frailty likely represents a closer approximation of biologic age than chronologic age, this may in part explain the strength of using frailty for risk prediction.[26]

It is important to note that, despite its strengths, use of this CFI is not intended to replace well-validated metrics for assessment of frailty status using in-person measurements. While health deficits related to one's frailty status were measured in the CoreValve trials, there were insufficient baseline data collected to generate a Fried index, and thus there was not a clear in-person reference standard to compare the CFI against. Furthermore, if CFIs are to be used in the clinical care of individual patients versus making broader population-based policy decisions, it would be necessary and important to evaluate the degree of misclassification of one's frailty status observed due to ascertainment of frailty via claims. As the Johns Hopkins CFI is not a perfect surrogate of the Fried index (area under the curve=0.75),[14] well-validated frailty metrics based on in-person measurements should be considered the gold standard for frailty assessment at the current time. Though over 20 different frailty scales have been developed,[28] regardless of the scale evaluated, frailty as a construct has been consistently associated with a 1.4- to 4.5-fold increased risk of adverse outcomes following TAVR, including short- and long-term mortality, prolonged hospital stay, and poor quality of life.[4,6,29–32] In the FRAILTY-AVR (Frailty in Older Adults Undergoing Aortic Valve Replacement) study, a prospective cohort of older adults undergoing AVR at 14 centers across 3 countries that compared 7 different frailty scales, the Essential Frailty Toolset was the strongest predictor of adverse outcomes, predicting a 3.7-fold increased risk of death and 2.1-fold risk of disability at 1 year and should be considered the first-line technique for evaluation of frailty in adults undergoing AVR.[1] While this brief 4-item scale, using chair rises, assessment of cognitive impairment, hemoglobin levels, and serum albumin to determine one's frailty status, is straightforward to implement, it may be challenging to collect the requisite data to calculate it retrospectively. Similarly, while many other frailty metrics (eg, Fried index, Short Physical Performance Battery, etc) represent validated techniques for assessing frailty in adults undergoing AVR and may be considered alternatives to the Essential Frailty Toolset, these may also be challenging to apply retrospectively.

While not a surrogate for such validated assessments of frailty, there are multiple circumstances in which frailty is unmeasured in which retrospective ascertainment of one's frailty status could be useful to improve risk stratification. As acquisition of in-person measures of frailty may be limited by time, expense, and availability, missing frailty information may be an important source of unmeasured risk. In these settings, CFIs may represent a valid alternative for identifying one's frailty status. As the current study indicates, in patients with severe aortic valve disease undergoing AVR, CFIs may capture relevant frailty information and thus allow retrospective classification of one's frailty status to aid in evaluation of this important subgroup. This could be used at a hospital or health-system level to identify populations of patients undergoing AVR for early mobilization, nutritional support, and intensive rehabilitation with the goal of possibly improving periprocedural outcomes or could be used for research to identify if observed effects are consistent across frailty groupings.[33–35]

As frailty is present in upwards of 60% of TAVR recipients (consistent with the findings from this study that 64.9% of individuals had frailty), it may represent an important unmeasured confounder in the valvular heart disease population and strongly influence treatment choice and outcomes.[35,36] In fact, consistent with prior observations that frailty may be a greater

effect modifier of high-risk interventions,[35] the Johns Hopkins CFI was associated with a greater magnitude of risk in the SAVR than TAVR population in the current study. Despite being associated with greater risk in SAVR versus TAVR, it is unknown if CFIs could validly be used to identify differential benefit from one procedure versus the other and, as such, propose these as future topics of investigation. While disability and weight loss have been shown to be the most important individual components of frailty to discriminate among those likely to have poor outcomes after TAVR,[31] it is unknown if these or other frailty-related factors also identify individuals with the most benefit from TAVR versus SAVR.

Our study has several limitations. First, we only evaluate a single CFI, and it is possible that other CFIs may perform differently. As other published CFIs require outpatient and durable medical equipment files that are not as commonly used or widely available, we chose to focus the current analysis on the CFI by Segal et al, which was validated against the Fried index, often considered the gold standard for physical frailty. Nevertheless, these findings may not generalize to other CFIs. Second, there were insufficient data to construct the Fried index from available variables, and thus the CFI cannot be compared with this index to demonstrate construct validity and investigate the degree of misclassification. Nevertheless, as the Johns Hopkins CFI associated with multiple individual markers of frailty and disability, it remains valid for use in the valvular disease population. Third, our analysis was limited to a specific group of studies of TAVR linked to Medicare claims. Thus, whether similar results would be observed with studies of other populations or non-Medicare claims is unclear. Fourth, because of overlapping age distributions between CFI tertiles, the effect of age cannot be removed despite adjustment. Fifth, though linked and nonlinked study participants were overall similar across a broad range of characteristics, it is possible that they are different across unmeasured characteristics that could influence the generalizability of the study results.

CONCLUSIONS

In linked Medicare and CoreValve study data, a CFI, anchored to a well-developed construct of phenotypic frailty, consistently identified individuals with greater impairments in in-person measures of frailty, disability, cognitive dysfunction, and malnutrition. The CFI identified individuals at higher risk of death, MACCE, hospitalization, and bleeding, independent of age and conventional risk metrics. These results that, while not a replacement for validated frailty assessments using in-person measurement, the use of CFIs to retrospectively ascertain frailty status in studies of aortic valve disease missing these assessments may be valid and capture prognostically relevant information over and above traditional risk metrics.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S12
Figure S1

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Supplemental Material

Table S1. Demographic, procedural, risk score, and comorbidity variables included in baseline CoreValve trial assessments.

Variable Domain	Variable
Demographics	Age
	Sex
Comorbidities	Diabetes mellitus
	Hypertension
	Peripheral vascular disease
	Prior cerebrovascular event or transient ischemic attack
	Coronary artery disease
	History of myocardial infarction
	Prior percutaneous coronary intervention
	Prior coronary artery bypass grafting
	History of pacemaker or implantable defibrillator
	Congestive heart failure
	Atrial flutter or fibrillation
	History of cirrhosis
	Connective tissue diseases
	Use of immunosuppressive therapy
Risk scores	Society of Thoracic Surgeons risk score
	Logistic EuroSCORE
	Charlson comorbidity index
Procedural variables	Number of valves implanted
	Arterial access site
	Severity of aortic calcification
	Presence of a chest wall deformity or hostile mediastinum

Table S2. Frailty-related variable included in baseline CoreValve trial assessments.

Variable Domain	Variable
Nutrition	Serum albumin < 3.3 g/dL
	Unplanned weight loss,
	History of anemia requiring transfusion
	Body mass index
Weakness/slowness	Presence of falls in the past 6 months
	5-meter walk time
	Grip strength below threshold
Cognitive Dysfunction	Mini-mental status exam score
Disability	Urinary incontinence
	Dependence in living
	Dependence in bathing
	Dependence in feeding
	Dependence in dressing
	Dependence in toileting
	Dependence in toileting
Functional status assessment	New York Heart Association class
	Kansas City Cardiomyopathy Questionnaire overall summary score
	Kansas City Cardiomyopathy Questionnaire clinical summary score
	EQ-5D
	12-item short form questionnaire, physical composite score
	12-item short form questionnaire, mental composite score
	36-item short form questionnaire, physical composite score
	36-item short form questionnaire, mental composite score
Severity of lung disease	Forced expiratory volume in 1-second (FEV1)
	Lung diffusing capacity for carbon monoxide (DLCO)
	Chronic lung severity classification
	Requirement for home oxygen use,

Table S3. Definition of Endpoints Used in the CoreValve Studies.

Variable	High Risk	SURTAVI
Primary Outcome	All cause mortality @ 12 mo	All cause death or disabling stroke @ 12 mo
Acute Kidney Injury	N/A	Stage 1 – Increase in serum creatinine to 150-199% (1.5-1.9 x increase compared with baseline) OR increase of ≥ 0.3 mg/dl (≥26.4 μmol/L) OR urine output <0.5 ml/kg/hour for >6 but <12 hours Stage 2 – Increase in serum creatinine to 200-299% (>2.0-2.9 x increase compared with baseline) OR urine output <0.5 ml/kg/hour for >12 but < 24 hours Stage 3 – Increase in serum creatinine to ≥300% (> 3 x increase compared with baseline) OR serum creatinine of > 4.0 mg/d (≥354 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L) OR urine output <0.3 ml/kg/hour for >24 hours OR anuria for > 12 hours Patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria. Stage 2 and 3 AKI is considered a serious adverse event.
Aortic Reintervention	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical reoperations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered reinterventions.	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical reoperations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered reinterventions.
Bleeding	Life Threatening or Disabling Bleeding • Fatal bleeding OR • Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR • Bleeding associated with a drop in hemoglobin of ≥5 g/dl or whole blood or packed red blood cells (RBCs) transfusion ≥4 units Major bleeding • Bleeding associated with either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood RBC AND does not meet criteria of life-threatening or disabling bleeding	Life-threatening or disabling bleeding • Fatal bleeding (BARC type 5) OR • Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b) OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR • Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells transfusion ≥4 units (BARC type 3b) Major Bleeding • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0g/dL or requiring transfusion of 2-3 units of whole blood/RBC, or causing hospitalization or permanent injury or requiring surgery AND • Does not meet criteria of life-threatening or disabling bleeding Minor Bleeding • Any bleeding worthy of clinical mention (eg. access site hematoma) that does not qualify as life-threatening, disabling or major "Overt" source of bleeding is defined by any of the following criteria being met: • Reoperation after closure of sternotomy for the purpose of controlling bleeding (BARC Type 4) • Chest tube output:

		• 2 L within a 24 hour period (BARC Type 4) OR • > 350 cc within 1st hr. post op OR • ≥ 250 cc. 2nd hr. post op OR • > 150 cc 3rd hr. post op • Bleeding from the vascular system outside of the access site (TAVR) • Bleeding from an access site that requires an intervention (TAVR) • Bleeding from the vascular system outside of the surgical site (Surgical replacement)
Death	<u>All-cause Death:</u> All deaths from any cause after a valve intervention. This includes all cardiovascular and non-cardiovascular deaths. <u>Cardiovascular Death:</u> • Any death due to a cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure) • Unwitnessed death and death of unknown cause • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure. Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease. <u>Non-cardiovascular death:</u> • Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma. <u>Valve-related death:</u> • Any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis; or related to reintervention on the operated valve.	<u>All-cause mortality:</u> All deaths from any cause after a valve intervention. This includes all cardiovascular and non-cardiovascular deaths. <u>Cardiovascular mortality:</u> Cardiovascular death will be defined according to the Valve Academic Research Consortium (VARC)-2; Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation (TAVI); 2012-10-09. A death meeting any one of the following criteria: • Death due to proximate cardiac cause (eg. myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause <u>Non-cardiovascular mortality:</u> Any death in which primary cause of death is clearly related to another condition (eg. trauma, cancer, suicide) NOTE: All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (eg. Cancer, infection) are classified as cardiac
Myocardial Infarction	<u>Peri-procedural MI (≤72 hours after the index procedure)</u> • New ischemic symptoms (e.g. chest pain or shortness of breath) or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes – either elevation >1 mm or depression >1 mm in two or more contiguous leads, hemodynamic instability; or imaging evidence of new loss of viable myocardium or new wall motion abnormality) • Elevated cardiac biomarkers evidence, (preferably CK-MB) within 72 hours after the index procedure, consisting of two or more post-procedure samples that are 6-8 hours apart with a 20% increase in the second sample and a peak value exceeding 10x the	N/A

	99th percentile upper reference limit (URL) or a peak value exceeding 5x the 99th percentile URL and with new pathological Q waves in at least 2 contiguous leads. <u>Spontaneous MI (>72 hours after the index procedure) including any of the following:</u> • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following: -ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block); -New pathological Q waves ≥2 contiguous leads; -Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality • Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.	
Neurologic event	<u>Stroke Diagnostic Criteria:</u> • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurologic deficit results in death • No other readily identifiable non-stroke cause for the clinical presentations (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)* • Confirmation of the diagnosis by at least one of the following: -Neurology or neurosurgical specialist -Neuroimaging procedure (MR or CT scan or cerebral angiography) -Lumbar puncture (spinal fluid analysis diagnostic of intracranial hemorrhage) <u>Stroke Definitions</u> *Transient ischemia attack* ▪ A new focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), and always within 24 hours. ▪ Neuroimaging without tissue injury	<u>Diagnostic Criteria</u> • Acute episode of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • *Stroke:* duration of a focal or global neurological deficit ≥ 24 hours; OR < 24 hours available neuroimaging documents a new hemorrhage or infarct; OR the neurologic deficit results in death • *TIA:* duration of a focal or global neurological deficit <24 hours, any variable neuroimaging does not demonstrate a new hemorrhage or infarct • No other readily identifiable non-stroke cause for the clinical presentations (eg. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with designated neurologist • Confirmation of the diagnosis by at least one of the following: ○ Neurology or neurosurgical specialist ○ Neuroimaging procedure (CT scan or brain MRI), but stroke be diagnosed on clinical grounds alone <u>Stroke Classification</u> • Ischemic: an acute episode of focal cerebral, spinal or retinal dysfunctions caused by infarction of the central nervous system tissue • Hemorrhagic: an acute episode of focal cerebral, spinal or spinal dysfunctions caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage

	Stroke (diagnosed as above, preferably with positive neuroimaging study) • Minor: Modified Rankin <2 at 30 and 90 days • Major: Modified Rankin ≥2 at 30 and 90 days	<u>Stroke Definitions</u> • Disabling stroke: an modified Rankin score (mRS) of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline • Non-disabling stroke: an mRS score of < 2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline

Table S4. ICD-9-CM claims used to create the Segal claims-based frailty index.

Component	ICD-9-CM Diagnosis Codes
Chronic heart failure	39891 402x1 404x3 428x
Parkinson`s disease	3320
Arthritis	7140 7141 7142 71430 71431 71432 71433 7144 71481 71489 7149 7200 71500 71504 71509 71510 71511 71512 71513 71514 71515 71516 71517 71518 71520 71521 71522 71523 71524 71525 71526 71527 71528 71530 71531 71532 71533 71534 71535 71536 71537 71538 71580 71589 71590 71591 71592 71593 71594 71595 71596 71597 71598 V134
Cognitive impairment	2900 29010 29011 29012 29013 29020 29021 2903 29040 29041 29042 29043 2908 2909 2930 2931 2940 2941 29410 29411 29420 29421 2948 2949 3100 3102 3108 31081 31089 3109 3310 3311 33111 33119 3312 33182 797
Depression	3090 3091 30922 30923 30924 30928 30929 3093 3094 30982 30983 30989 3099 29383 29600 29601 29602 29603 29604 29605 29606 29610 29611 29612 29613 29614 29615 29616 29620 29621 29622 29623 29624 29625 29626 29630 29631 29632 29633 29634 29635 29636 29640 29641 29642 29643 29644 29645 29646 29650 29651 29652 29653 29654 29655 29656 29660 29661 29662 29663 29664 29665 29666 2967 29680 29681 29682 29689 29690 29699 3004 311
Falls	E8800 E8801 E8809 E8810 E8811 E882 E8830 E8831 E8832 E8839 E8840 E8841 E8842 E8843 E8844 E8845 E8846 E8849 E885 E8850 E8851 E8852 E8853 E8854 E8859 E8860 E8869 E888 E8880 E8881 E8888 E8889 E9681 E9870 E9871 E9872 E9879
Impaired mobility	V463
Musculoskeletal problems	7130 7131 7132 7133 7134 7135 7136 7137 7138 71600 71601 71602 71603 71604 71605 71606 71607 71608 71609 71620 71621 71622 71623 71624 71625 71626 71627 71629 71629 71630 71631 71632 71633 71634 71635 71636 71637 71638 71639 71640 71641 71642 71643 71644 71645 71646 71647 71648 71649 71650 71651 71652 71653 71654 71655 71656 71657 71658 71659 71660 71661 71662 71663 71664 71665 71666 71667 71668 71680 71681 71862 71683 71684 71685 71686 71687 71688 71689 71690 71691 71692 71693 71694 71695 71696 71697 71698 71699 71810 71811 71812 71813 71814 71815 71817 71818 71819 71820 71821 71822 71823 71824 71825 71826 71827 71828 71829 71850 71851 71852 71853 71854 71855 71856 71857 71858 71859 71860 71865 71870 71871 71872 71873 71874 71875 71876 71877 71878 71879 71880 71881 71882 71883 71884 71885 71886 71887 71888 71889 71890 71891 71892 71893 71894 71895 71897 71898 71899 71900 71901 71902 71903 71904 71905 71906 71907 71908 71909 71910 71911 71912 71913 71914 71915 71916 71917 71918 71919 71920 71921 71922 71923 71924 71925 71926 71927 71928 71929 71930 71931 71932 71933 71934 71935 71936 71937 71938 71939 71940 71941 71942 71943 71944 71945 71946 71947 71948 71949 71950 71951 71952 71953 71954 71955 71956 71957 71958 71959 71960 71961 71962 71963 71964 71965 71966 71967 71968 71969 7197 71970 71975

	71976 71977 71978 71979 71980 71981 71982 71983 71984 71985 71986 71987 71988 71989 71990 71991 71992 71993 71994 71995 71996 71997 71998 71999 7201 7202 72081 72089 7209 7210 7211 7212 7213 72141 72142 7215 7216 7217 7218 72190 72191 7220 72210 72211 7222 72230 72231 72232 72239 7224 72251 72252 7226 72270 72271 72272 72273 72280 72281 72282 72283 72290 72291 72292 72293 7230 7231 7232 7233 7234 7235 7236 7237 7238 7239 72400 72401 72402 72403 72409 7241 7242 7243 7244 7245 7246 72470 72471 72479 7248 7249 73300 73301 73302 73393 73309 7331 73310 73311 73312 73313 73314 73315 73316 73319 73393 73394 73395 73396 73397 73398 V1351 4350 4351 4352 4353 4358 4359
Paranoia	29381 29382 29500 29501 29502 29503 29504 29505 29510 29511 29512 29513 29514 29515 29520 29521 29522 29523 29524 29525 29530 29531 29532 29533 29534 29535 29540 29541 29542 29543 29544 29545 29550 29551 29552 29553 29554 29555 29560 29561 29562 29563 29564 29565 29570 29571 29572 29573 29574 29575 29580 29581 29582 29583 29584 29585 29590 29591 29592 29593 29594 29595 2970 2971 2972 2973 2978 2979 2980 2981 2982 2983 2984 2988 2989
Mycoses	1100 1101 1102 1103 1104 1105 1106 1108 1109 1110 1111 1112 1113 1118 1119 1120 1121 1122 1123 1125 11282 11284 11285 11289 1129 1141 1143 1149 11500 11509 11510 11519 11590 11599 1160 1161 1162 1170 1171 1172 1173 1174 1175 1176 1177 1178 1179 118
Urinary tract infections	03284 59000 59001 59010 59011 5902 5903 59080 59081 5909 5950 5951 5952 5953 5954 59581 59582 59589 5959 5970 59780 59781 59789 59800 59801 5990
Gout or other crystal-induced arthropathy	2740 27400 27401 27402 27403 27410 27411 27419 27481 27482 27489 2749 71210 71211 71212 71213 71214 71215 71216 71217 71218 71219 71220 71221 71222 71223 71224 71225 71226 71227 71228 71229 71230 71231 71232 71233 71234 71235 71236 71237 71238 71239 71280 71281 71282 71283 71284 71285 71286 71287 71288 71289 71290 71291 71292 71293 71294 71295 71296 71297 71298 71299
Skin and soft tissue infections	0201 0210 0220 0311 03285 035 0390 6800 6801 6802 6803 6804 6805 6806 6807 6808 6809 68100 68101 68102 68110 68111 6819 6820 6821 6822 6823 6824 6825 6826 6827 6828 6829 684 6850 6851 6860 68600 68601 68609 6861 6868 6869
Chronic skin ulcer	7070 70700 70701 70702 70703 70704 70705 70706 70707 70709 7071 70710 70711 70712 70713 70714 70715 70719 70720 70721 70722 70723 70724 70725 7078 7079
Pneumonia	00322 0203 0204 0205 0212 0221 0310 0391 0521 0551 0730 0830 1124 1140 1144 1145 11505 11515 11595 1304 1363 4800 4801 4802 4803 4808 4809 481 4820 4821 4822 4823 48230 48231 48232 48239 4824 48240 48241 48242 48249 4828 48281 48282 48283 48284 48289 4829 483 4830 4831 4838 4841 4843 4845 4846 4847 4848 485 486 5130 5171
Charlson Comorbidity Index	
Component	**ICD-9-CM Diagnosis Codes**

Timing: Prior to or on the procedure date	
Myocardial infarction	"412"
Peripheral vascular disease	"441x","4439","7854","V434"
Cerebrovascular disease	"438"
Dementia	"290x"
Chronic pulmonary disease	"490","491","492","493","494","495","496","500","501","502","503","504","505,"5064"
Rheumatologic disease	"725","7100","7101","7104","7140","7141","7142", "71481"
Peptic ulcer disease	"5314x","5315x","5316x","5317x","5324x","5325x","5326x","5327x","5334x","5335x","5336x","5337x","5344x","5345x","5346x","5347x"
Mild liver disease	"5716x","5712","5714","5715"
Diabetes (mild to moderate)	"2500x","2501x","2502x","2503x","2507x"
Diabetes with chronic complications	"2504x","2505x","2506x"
Hemiplegia or paraplegia	"342x","3441"
Renal disease	"582x","588x","5830","5831","5832","5833","5834","5835","5836","5837","585","586"
Moderate or severe liver disease	"4560x","4561x","4562x", "5722","5723","5724","5725","5726","5727","5728","5729","5730","5731","5732","5733","5734","5735","5736","5737","5738","5739","5740","5741","5742","5743","5744","5745","5746","5747","5748","5749","5750","5751","5752","5753","5754","5755","5756","5757","5758","5759","5760","5761","5762","5763","5764","5765","5766","5767","5768","5769","5770","5771","5772","5773","5774","5775","5776","5777","5778","5779","5780","5781","5782","5783","5784","5785","5786","5787","5788","5789", "5790","5791","5792","5793","5794","5795","5796","5797","5798","5799","5800","5801","5802","5803","5804","5805","5806","5807","5808","5809","5810","5811","5812","5813","5814","5815","5816","5817","5818","5819","5820","5821","5822","5823","5824","5825","5826","5827","5828"
Timing: Prior to the procedure date	
Myocardial infarction	"410xx"
Congestive heart failure	"428x"
Cerebrovascular disease	"430x","431x","432x","433x","434x","435x","436x","437x"
Peptic ulcer disease	"5310x","5311x","5312x","5313x","5320x","5321x","5322x","5323x","5330x","5331x","5332x","5333x","5340x","5341x","5342x","5343x","5319","5329","5339","5349"
Any malignancy, including lymphoma and leukemia	"140x","141x","142x","143x","144x","145x","146x","147x","148x","149x","150x","151x","152x","153x","154x","155x","156x","157x","158x","159x","160x","161x","162x","163x","164x","165x","166x","167x","168x","169x","170x","171x","172x","174x","175x","176x","177x","178x","179x","180x","181x","182x","183x","184x","185x","186x","187x","188x","189x","190x","191x","192x","193x","194x","195x","200xx","201xx","202xx","203xx","204xx","205xx","206xx","207xx","208xx"

Metastatic solid tumor	"196x","197x","198x","199x"
AIDS	"042x","043x","044x"
Peripheral vascular disease	ICD-9-CM procedure code "3848"

International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) claims used to create the Segal frailty index as per Segal JB, Chang HY, Du Y, Walston JD, Carlson MC, Varadhan R. Development of a Claims-based Frailty Indicator Anchored to a Well-established Frailty Phenotype. *Med Care* 2017;55:716-722.

Table S5. Characteristics of Linked and Non-Linked Individuals Included in the EXTEND Study.

Characteristic	Linked group (N = 4230)	Non-linked group (N = 1072)	p-value
Age (years)	83.0 ± 6.7	82.4 ± 7.1	0.02
Female sex — no. (%)	1939 (45.8)	478 (44.6)	0.47
Body Mass Index (kg/m^2)	28.2 ± 6.2	28.3 ± 6.4	0.14
New York Heart Association class — no. (%)			0.69
Class II	811 (19.2)	218 (20.3)	
Class III	2781 (65.7)	696 (20.0)	
Class IV	638 (15.1)	158 (19.9)	
Society of Thoracic Surgeons Risk Score (%)	7.9 ± 4.5	7.5 ± 4.4	0.02
Logistic EuroSCORE (%)	19.5 ± 14.6	20.0 ± 15.7	0.0011
Diabetes mellitus — no. (%)			
All	1585 (37.5)	400 (37.3)	0.94
Controlled by insulin	545 (12.9)	143 (13.3)	0.68
History of hypertension — no. (%)	3955 (93.5)	1000 (93.3)	0.80
Peripheral vascular disease — no. (%)	1787 (42.4)	474 (44.2)	0.28
Prior stroke — no. (%)	496 (11.7)	113 (10.6)	0.28
Prior transient ischemic attack — no. (%)	425 (10.1)	93 (8.7)	0.19
Cardiac risk factors— no. (%)			
Coronary artery disease	3189 (75.4)	813 (75.8)	0.76
Prior coronary-artery bypass surgery	1315 (31.1)	320 (29.9)	0.46
Prior percutaneous coronary intervention	1468 (34.7)	364 (34.0)	0.65
Balloon Valvuloplasty	417 (9.9)	98 (9.1)	0.53
Pre-Existing Pacemaker of Implantable Cardioverter-Defibrillator	818 (19.3)	234 (21.8)	0.07
Prior myocardial infarction	1025 (24.2)	252 (23.5)	0.63
Congestive heart failure	4126 (97.5)	1033 (96.4)	0.04
Prior atrial fibrillation or atrial flutter	1711 (40.5)	427 (39.9)	0.73

Represents a comparison of individuals linked and non-linked to Medicare claims in the US CoreValve Pivotal Trials dataset as part of the Extending Trial-Based Evaluations of Medical Therapies Using Novel Sources of Data
(EXTEND) study. The 4230 linked individuals includes 600 individuals from the CoreValve High Risk trial, 421 from the US CoreValve Extreme Risk study, 915 from the High Risk Continued Access Study, and 1005 from Surgery or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients (SURTAVI) trial. The non-linked group represents the baseline characteristics of individuals whose CoreValve study data could and could not be linked to Medicare claims. All values are listed as means ± standard deviations unless otherwise indicated. no. = number.

Reproduced with permission from Strom JB, Faridi KF, Butala NM, Zhao Y, Tamez H, Valsdottir LR, Brennan JM, Shen C, Popma JJ, Kazi DS, Yeh RW. Use of Administrative Claims to Assess Outcomes and Treatment Effect in Randomized Clinical Trials for Transcatheter Aortic Valve Replacement: Findings from the EXTEND Study. Circulation. 2020 Jul 21; 142(3):203-213.

Table S6. Comparison of Outcomes by CFI Tertile in the Medicare-linked CoreValve High Risk Trial (N = 600)

Outcomes	Tertile 1 (N = 151)	Tertile 2 (N = 206)	Tertile 3 (N = 243)	HR (95% CI) for Tertile 2 vs. 1	p-value*	HR (95% CI) for Tertile 3 vs. 1	p-value†
Death (N = 230) – no. (%)	50 (33.1)	64 (31.1)	116 (47.7)	0.91 (0.65-1.27)	0.91	1.57 (1.16-2.13)	0.004
MACCE (N = 276) – no. (%)	66 (43.7)	86 (41.8)	124 (51.0)	0.92 (0.69-1.22)	0.54	1.24 (0.95-1.63)	0.12
Acute kidney injury (N = 70) – no. (%)	17 (11.3)	25 (12.1)	28 (11.5)	1.06 (0.58-1.96)	0.84	1.02 (0.56-1.85)	0.96
Bleeding (N = 279) – no. (%)	62 (41.1)	91 (44.2)	126 (51.9)	1.05 (0.78-1.43)	0.73	1.29 (0.97-1.71)	0.08
Stroke or transient ischemic attack (N = 100) – no. (%)	30 (19.9)	33 (16.0)	37 (15.2)	0.80 (0.49-1.28)	0.35	0.76 (0.48-1.22)	0.26
Myocardial Infarction (N =14) – no. (%)	< 11	< 11	< 11	0.73 (0.24-2.24)	0.58	0.21 (0.04-1.01)	0.05
Aortic reintervention (N < 11) – no. (%)	< 11	< 11	< 11	2.94 (0.33-26.16)	0.33	1.25 (0.11-13.73)	0.86
Hospitalization (N = 130) – no. (%)	33 (21.9)	52 (25.2)	45 (18.5)	1.18 (0.78-1.77)	0.44	0.87 (0.57-1.33)	0.51
Other (N = 24) – no. (%)	< 11	< 11	< 11	0.84 (0.31-2.28)	0.73	0.80 (0.30-2.12)	0.65

*Represents the p-value for the comparison of CFI tertile 2 vs. tertile 1. †Represents the p-value for the comparison of CFI tertile 3 vs. tertile 1. Listed is the number and percentage of outcomes in each category occurring within 1-year from procedure by CFI tertile in the CoreValve High Risk Trial. Percentages are determined using Kaplan-Meier estimates. Additionally, the hazard ratios and 95% confidence intervals for the comparison of tertile 2 vs. 1 and tertile 3 vs. 1 are listed with the log-rank p-values for these comparisons. For non-death outcomes, estimates are adjusted for the competing risk of death using Fine-Gray subdistribution hazard models. Cell numbers < 11 are suppressed from publication per CMS policy. CFI = claims-based frailty index, CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular events, no. = number.

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Table S7. Comparison of Outcomes by CFI Tertile in the Medicare-linked CoreValve Continued Access Study (N = 915).

Outcomes	Tertile 1 (N = 207)	Tertile 2 (N = 304)	Tertile 3 (N = 404)	HR (95% CI) for Tertile 2 vs. 1	p-value*	HR (95% CI) for Tertile 3 vs. 1	p-value†
Death (N = 230) – no. (%)	46 (22.2)	78 (25.7)	106 (26.2)	1.16 (0.81-1.67)	0.41	1.18 (0.84-1.66)	0.35
MACCE (N = 291) – no. (%)	61 (29.5)	99 (32.6)	131 (32.4)	1.12 (0.92-1.53)	0.49	1.10 (0.81-1.48)	0.55
Acute kidney injury (N = 103) – no. (%)	25 (12.1)	36 (11.8)	42 (10.4)	0.98 (0.59-1.62)	0.94	0.86 (0.53-1.39)	0.53
Bleeding (N = 367) – no. (%)	68 (32.9)	126 (41.5)	173 (42.8)	1.33 (1.01-1.75)	0.04	1.37 (1.06-1.77)	0.02
Stroke or transient ischemic attack (N = 117) – no. (%)	30 (14.5)	33 (10.9)	54 (13.4)	0.74 (0.46-1.21)	0.23	0.92 (0.59-1.43)	0.72
Myocardial Infarction (N =19) – no. (%)	< 11	< 11	< 11	1.82 (0.49-6.85)	0.37	1.37 (0.36-5.13)	0.64
Aortic reintervention (N < 11) – no. (%)	< 11	< 11	< 11	0.68 (0.10-4.82)	0.70	1.03 (0.19-5.59)	0.97
Hospitalization (N = 170) – no. (%)	32 (15.5)	61 (20.1)	77 (19.1)	1.34 (0.88-2.04)	0.18	1.25 (0.83-1.88)	0.28
Other (N = 30) – no. (%)	< 11	12 (4.0)	< 11	1.02 (0.42-2.47)	0.96	0.64 (0.25-1.60)	0.34

*Represents the p-value for the comparison of CFI tertile 2 vs. tertile 1. †Represents the p-value for the comparison of CFI tertile 3 vs. tertile 1. Listed is the number and percentage of outcomes in each category occurring within 1-year from procedure by CFI tertile in the Continued Access Study. Percentages are determined using Kaplan-Meier estimates. Additionally, the hazard ratios and 95% confidence intervals for the comparison of tertile 2 vs. 1 and tertile 3 vs. 1 are listed with the log-rank p-values for these comparisons. For non-death outcomes, estimates are adjusted for the competing risk of death using Fine-Gray subdistribution hazard models. Cell numbers < 11 are suppressed from publication per CMS policy. CFI = claims-based frailty index, CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular events, no. = number.

Table S8. Comparison of Outcomes by CFI Tertile in the Medicare-linked CoreValve SURTAVI study (N = 842)

Outcomes	Tertile 1 (N = 429)	Tertile 2 (N = 278)	Tertile 3 (N = 135)	HR (95% CI) for Tertile 2 vs. 1	p-value*	HR (95% CI) for Tertile 3 vs. 1	p-value†
Death (N = 119) – no. (%)	56 (13.1)	40 (14.4)	23 (17.0)	1.11 (0.75-1.65)	0.59	1.35 (0.84-2.16)	0.22
MACCE (N = 198) – no. (%)	92 (21.5)	74 (26.6)	32 (23.7)	1.30 (0.97-1.75)	0.08	1.15 (0.77-1.69)	0.50
Acute kidney injury (N = 104) – no. (%)	60 (14.0)	26 (9.4)	18 (13.3)	0.65 (0.42-1.02)	0.06	0.95 (0.57-1.60)	0.85
Bleeding (N = 168) – no. (%)	85 (19.8)	52 (18.7)	31 (23.0)	0.95 (0.68-1.32)	0.74	1.21 (0.81-1.81)	0.36
Stroke or transient ischemic attack (N = 100) – no. (%)	40 (9.3)	42 (15.1)	18 (13.3)	1.68 (1.09-2.57)	0.02	1.46 (0.84-2.52)	0.18
Myocardial Infarction (N =23) – no. (%)	< 11	< 11	< 11	1.39 (0.54-3.60)	0.50	2.14 (0.77-5.96)	0.15
Aortic reintervention (N = 18) – no. (%)	12 (2.8)	< 11	0 (0.0)	0.77 (0.29-2.05)	0.60	N/A	N/A
Hospitalization (N = 131) – no. (%)	59 (13.8)	44 (15.8)	28 (20.7)	1.16 (0.80-1.70)	0.43	1.57 (1.02-2.43)	0.04
Other (N = 20) – no. (%)	< 11	< 11	< 11	0.98 (0.38-2.52)	0.97	0.58 (0.13-2.59)	0.47

*Represents the p-value for the comparison of CFI tertile 2 vs. tertile 1. †Represents the p-value for the comparison of CFI tertile 3 vs. tertile 1. Listed is the number and percentage of outcomes in each category occurring within 1-year from procedure by CFI tertile in the SURTAVI trial. Percentages are determined using Kaplan-Meier estimates. Additionally, the hazard ratios and 95% confidence intervals for the comparison of tertile 2 vs. 1 and tertile 3 vs. 1 are listed with the log-rank p-values for these comparisons. For non-death outcomes, estimates are adjusted for the competing risk of death using Fine-Gray subdistribution hazard models. Cell numbers < 11 are suppressed from publication per CMS policy. CFI = claims-based frailty index, CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular events, no. = number.

Table S9. Results of Proportional Hazards Regression using CFI as a Continuous Measure.

Outcome	HR (95% CI)	p-value
Death	1.31 (1.21-1.40)	< 0.001
MACCE	1.18 (1.11-1.26)	< 0.001
Acute kidney injury	0.94 (0.84-1.07)	0.36
Bleeding	1.21 (1.14-1.28)	< 0.001
Stroke or transient ischemic attack	1.09 (0.98-1.21)	0.10
Myocardial Infarction	0.89 (0.70-1.13)	0.33
Aortic reintervention	0.76 (0.49-1.18)	0.23
Hospitalization	1.09 (1.00-1.18)	0.053
Other	1.00 (0.79-1.25)	0.98

Listed is the hazard ratio, 95% CI confidence interval, and log-rank p-value for a 1-standard deviation increase in CFI for each outcome. For non-death outcomes, estimates are adjusted for the competing risk of death using Fine-Gray subdistribution hazard models. CFI = claims-based frailty index, CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular events no. = number.

Table S10. Comparison of Outcomes by CFI Tertile Amongst TAVR Recipients (N = 1656)

Outcomes	Tertile 1 (N = 497)	Tertile 2 (N = 575)	Tertile 3 (N = 584)	HR (95% CI) for Tertile 2 vs. 1	p-value*	HR (95% CI) for Tertile 3 vs. 1	p-value†
Death (N = 414) – no. (%)	100 (20.1)	138 (24.0)	176 (30.1)	1.22 (0.95-1.57)	0.12	1.57 (1.24-2.00)	< 0.001
MACCE (N = 539) – no. (%)	141 (28.4)	192 (33.4)	206 (353)	1.22 (0.99-1.51)	0.06	1.29 (1.05-1.58)	0.02
Acute kidney injury (N = 155) – no. (%)	50 (10.1)	52 (9.0)	53 (9.1)	0.90 (0.61-1.32)	0.57	0.90 (0.61-1.32)	0.58
Bleeding (N = 602) – no. (%)	142 (28.6)	204 (35.5)	256 (43.8)	1.30 (1.06-1.59)	0.01	1.66 (1.37-2.01)	< 0.001
Stroke or transient ischemic attack (N = 211) – no. (%)	59 (11.9)	79 (13.7)	73 (12.5)	1.17 (0.84-1.64)	0.35	1.06 (0.76-1.49)	0.74
Myocardial Infarction (N = 41) – no. (%)	< 11	19 (3.3)	12 (2.1)	1.66 (0.77-3.56)	0.19	1.02 (0.44-2.35)	0.96
Aortic reintervention (N = 28) – no. (%)	13 (2.6)	< 11	< 11	0.60 (0.26-1.39)	0.23	0.39 (0.15-1.03)	0.06
Hospitalization (N = 318) – no. (%)	85 (17.1)	115 (20.0)	118 (20.2)	1.20 (0.91-1.57)	0.19	1.22 (0.93-1.60)	0.15
Other (N = 48) – no. (%)	15 (3.0)	17 (3.0)	16 (2.7)	0.98 (0.49-1.95)	0.95	0.91 (0.45-1.82)	0.79

*Represents the p-value for the comparison of CFI tertile 2 vs. tertile 1. †Represents the p-value for the comparison of CFI tertile 3 vs. tertile 1. Listed is the number and percentage of outcomes in each category occurring within 1-year from procedure by CFI tertile in the overall cohort amongst those who received TAVR. Percentages are determined using Kaplan-Meier estimates. Additionally, the hazard ratios and 95% confidence intervals for the comparison of tertile 2 vs. 1 and tertile 3 vs. 1 are listed with the log-rank p-values for these comparisons. For non-death outcomes, estimates are adjusted for the competing risk of death using Fine-Gray subdistribution hazard models. Cell numbers < 11 are suppressed from publication per CMS policy. CFI = claims-based frailty index, CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular events, no. = number; TAVR = transcatheter aortic valve replacement.

Table S11. Comparison of Outcomes by CFI Tertile Amongst SAVR Recipients (N = 701).

Outcomes	Tertile 1 (N = 290)	Tertile 2 (N = 213)	Tertile 3 (N = 198)	HR (95% CI) for Tertile 2 vs. 1	p-value*	HR (95% CI) for Tertile 3 vs. 1	p-value†
Death (N = 165) – no. (%)	52 (17.9)	44 (20.7)	69 (34.9)	1.14 (0.78-1.66)	0.51	2.14 (1.51-3.02)	< 0.001
MACCE (N = 219) – no. (%)	78 (26.9)	67 (31.5)	81 (40.9)	1.17 (0.86-1.59)	0.31	1.68 (1.25-2.26)	< 0.001
Acute kidney injury (N = 122) – no. (%)	52 (17.9)	35 (16.4)	35 (17.7)	0.89 (0.59-1.35)	0.58	0.97 (0.64-1.48)	0.90
Bleeding (N = 212) – no. (%)	73 (25.2)	65 (30.5)	74 (37.4)	1.23 (0.90-1.69)	0.20	1.61 (1.18-2.19)	0.003
Stroke or transient ischemic attack (N = 106) – no. (%)	41 (14.1)	29 (13.6)	36 (18.2)	0.96 (0.60-1.54)	0.87	1.32 (0.85-2.05)	0.22
Myocardial Infarction (N = 15) – no. (%)	< 11	< 11	< 11	0.51 (0.14-1.90)	0.31	0.74 (0.22-2.44)	0.62
Hospitalization (N = 113) – no. (%)	39 (13.5)	42 (19.7)	32 (16.2)	1.50 (0.99-2.28)	0.06	1.23 (0.78-1.94)	0.37
Other (N = 26) – no. (%)	< 11	< 11	< 11	1.24 (0.53-2.89)	0.62	0.66 (0.23-1.90)	0.44

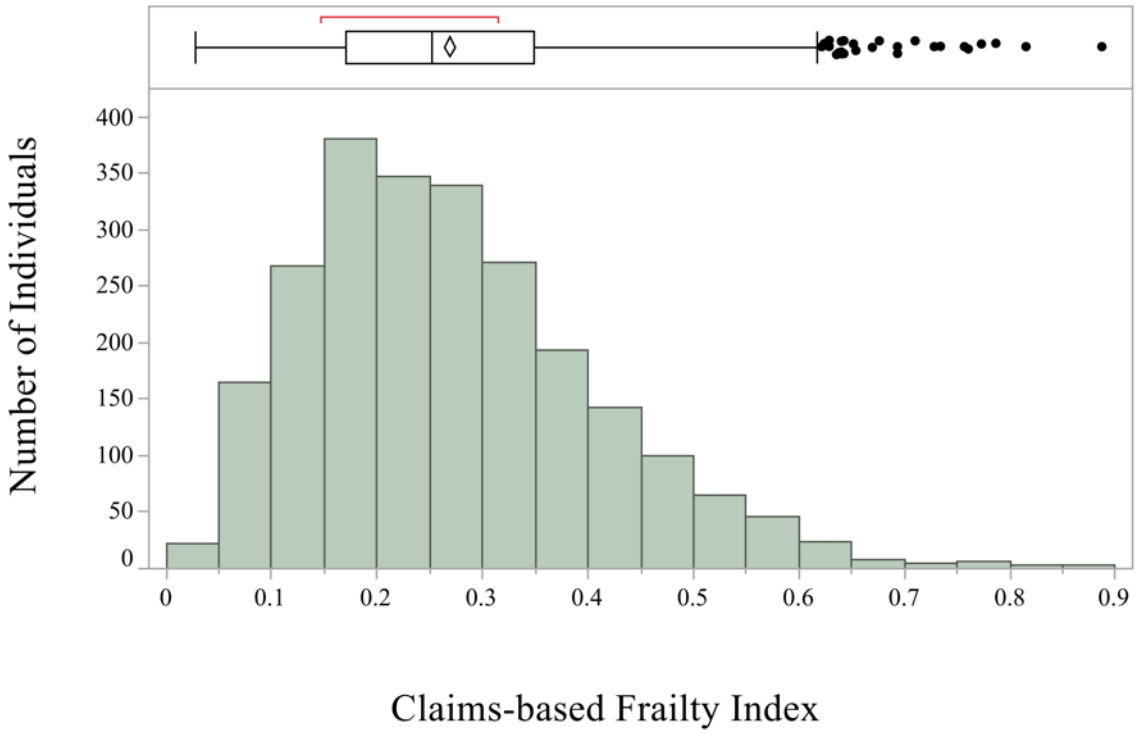
*Represents the p-value for the comparison of CFI tertile 2 vs. tertile 1. †Represents the p-value for the comparison of CFI tertile 3 vs. tertile 1. Listed is the number and percentage of outcomes in each category occurring within 1-year from procedure by CFI tertile in the overall cohort amongst those who received SAVR. Percentages are determined using Kaplan-Meier estimates. Additionally, the hazard ratios and 95% confidence intervals for the comparison of tertile 2 vs. 1 and tertile 3 vs. 1 are listed with the log-rank p-values for these comparisons. There were not enough individuals in each tertile to calculate hazard ratios for aortic reintervention. For non-death outcomes, estimates are adjusted for the competing risk of death using Fine-Gray subdistribution hazard models. Cell numbers < 11 are suppressed from publication per CMS policy. CFI = claims-based frailty index, CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular events, no. = number; SAVR = surgical aortic valve replacement.

Table S12. Comparison of Outcomes by CFI Tertile After Multivariable Adjustment

Outcomes	Adjusted HR (95% CI) for Tertile 2 vs. 1	p-value*	Adjusted HR (95% CI) for Tertile 3 vs. 1	p-value†
Death (N = 579) – no. (%)	1.13 (0.88-1.45)	0.33	1.48 (1.12-1.96)	0.006
MACCE (N = 765) – no. (%)	1.16 (0.94-1.42)	0.16	1.25 (0.99-1.59)	0.06
Acute kidney injury (N = 277) – no. (%)	1.08 (0.77-1.50)	0.67	1.25 (0.84-1.87)	0.28
Bleeding (N = 814) – no. (%)	1.21 (1.00-1.46)	0.06	1.40 (1.12-1.75)	0.004
Stroke or transient ischemic attack (N = 317) – no. (%)	1.06 (0.78-1.44)	0.73	1.06 (0.74-1.52)	0.77
Myocardial Infarction (N = 56) – no. (%)	1.61 (0.79-3.27)	0.19	1.37 (0.53-3.54)	0.51
Aortic reintervention (N = 33) – no. (%)	1.09 (0.36-3.27)	0.88	0.69 (0.19-2.42)	0.56
Hospitalization (N = 431) – no. (%)	1.53 (1.16-2.01)	0.002	1.56 (1.12-2.17)	0.008
Other (N = 74) – no. (%)	0.90 (0.50-1.62)	0.73	0.57 (0.27-1.19)	0.13

*Represents the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for a comparison of CFI tertiles for the primary and secondary endpoints as listed in the overall cohort. Estimates are adjusted for age, sex, New York Heart Association (NYHA) class, and Society of Thoracic Surgeons (STS) risk score. CFI = claims-based frailty index, CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular events, no. = number.

Figure S1. Histogram and box and whisker plot demonstrating the distribution of the claims-based frailty index in the linked dataset.



Represents a histogram displaying the number of individuals in the sample (y-axis) with each value of the claims-based frailty index (x-axis). A box and whisker plot indicates the interquartile range (box), median value (line separating the box into two parts) and range of values (whiskers).