Supplementary Material

Do frailty measures improve prediction of mortality and morbidity following transcatheter aortic valve implantation? An analysis of the UK TAVI registry
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Supplementary Methods

Mathematical Details of Model Updating Techniques

Let $P$ denote the number of predictors that are included in an existing TAVI CPM. Then the $j^{th}$ existing TAVI CPM provides a linear predictor (LP) on the logit scale of the form

$$\text{LP}_{i,j} = \beta_{0,j} + \sum_{p=1}^{P} \beta_{p,j} x_{i,p}$$

for patient $i$, covariates $x_{i,p}$ for $p \in [1, P]$, and associated coefficients $\beta_{p,j}$.

Then model updating methods, as previously described [1–4], have a hierarchical structure to alter an existing CPM to a new population. This study considered the addition of new variables that were not included in the original TAVI CPMs (i.e. frailty). Specifically, model updating of the $j^{th}$ existing TAVI CPM fits a logistic regression model in the UK TAVI registry with the $j^{th}$ existing LP and a frailty indicator as the only covariates, by modelling

$$\log \left( \frac{\pi_i}{1 - \pi_i} \right) = \hat{\alpha}_0 + \hat{\alpha}_1 \text{LP}_{i,j} + \delta_{\text{Frailty}} x_{i,\text{Frailty}}$$

(1)

where $\pi_i$ denotes the predicted event probability for patient $i$ in the UK TAVI registry, $x_{i,\text{Frailty}}$ is either KATZ, CSHA or poor mobility indication, and $\delta_{\text{Frailty}}$ is the corresponding coefficient estimate. The parameters $\hat{\alpha}_0$ and $\hat{\alpha}_1$ are the calibration intercept and slope, respectively.

This process was repeated for all three of the frailty measures individually and across all of the considered TAVI CPMs. Additionally, to explore the incremental benefit of adding the frailty measures into the TAVI CPMs, we iteratively added each of the frailty measures into Equation (1), under a likelihood ratio test selection criterion until all those frailty measures that significantly improved model fit were selected.

All models were fit in each multiple imputed dataset separately, with the coefficient estimates then pooled according to Rubin’s rules. Predictions were then made for each patient in the UK registry, using the pooled coefficient estimates. Subsequent performance estimates (e.g. area under the ROC curve) were made in each imputed dataset, which were then pooled using Rubin’s rules.
Supplementary Figures and Tables

**Supplementary Figure 1**: Distribution of the CSHA frailty score (left panel) and the crude 30-day mortality rate (right panel)
Supplementary Figure 2: Distribution of the KATZ frailty score (left panel) and the crude 30-day mortality rate (right panel)
Supplementary Figure 3: Proportion of patients defined as having CSHA-estimated frailty, KATZ activities of daily living dependency, or physician-estimated poor mobility per NHS England region and Wales. The sample size of each region is also depicted.
**Supplementary Table 1.** Baseline characteristics across the patients included and excluded in the analysis.

| Variable                                      | Included (n=2624) | Excluded (n=449) | p-value |
|-----------------------------------------------|-------------------|------------------|---------|
| Age, mean (SD)                                | 81.2 (7.58)       | 80.6 (7.78)      | 0.127   |
| Female, n (%)                                 | 1192 (45.4)       | 201 (44.8)       | 0.807   |
| Diabetic, n (%)                               | 641 (24.4)        | 97 (21.6)        | 0.573   |
| Smoker, n (%)                                 | 1316 (50.2)       | 193 (43.0)       | 0.227   |
| Creatinine, mean (SD)                         | 110.9 (60.5)      | 111.0 (61.2)     | 0.962   |
| Renal Failure *, n (%)                        | 143 (5.45)        | 28 (6.24)        | 0.270   |
| Previous MI, n (%)                            | 558 (21.3)        | 96 (21.4)        | 0.506   |
| Pulmonary Disease, n (%)                      | 791 (30.1)        | 110 (24.5)       | 0.115   |
| Neurological Disease, n (%)                   | 441 (16.8)        | 69 (15.4)        | 0.932   |
| Extracardiac Arteriopathy, n (%)              | 555 (21.2)        | 77 (17.1)        | 0.227   |
| Calcification of Ascending Aorta, % (n)       | 378 (14.4)        | 39 (8.69)        | 0.005   |
| Atrial Fibrillation, n (%)                    | 700 (26.7)        | 114 (25.4)       | 0.837   |
| Previous Cardiac Surgery, n (%)               | 799 (30.4)        | 109 (24.3)       | 0.062   |
| Previous PCI, n (%)                           | 524 (20.0)        | 86 (19.2)        | 0.903   |
| Height, mean (SD)                             | 1.64 (0.10)       | 1.66 (0.10)      | 0.020   |
| Weight, mean (SD)                             | 75.0 (17.1)       | 76.2 (17.4)      | 0.209   |
| CCS Class 4, n (%)                            | 24 (0.91)         | 7 (1.56)         | 0.243   |
| NYHA ≥ III, n (%)                             | 1985 (75.6)       | 347 (77.3)       | 0.001   |
| Aortic Valve Area, mean (SD)                  | 0.69 (0.23)       | 0.68 (0.23)      | 0.468   |
| Aortic Valve Peak Gradient, mean (SD)         | 71.2 (26.2)       | 72.9 (24.4)      | 0.243   |
| LVEF < 50%, n (%)                             | 948 (36.1)        | 161 (35.9)       | 0.474   |
| One or more diseased vessels, n (%)           | 1058 (40.3)       | 151 (33.6)       | 0.064   |
| Left Main Stem Disease, n (%)                 | 103 (3.93)        | 18 (4.01)        | 0.866   |
| Non-elective Procedure, n (%)                 | 365 (13.9)        | 62 (13.8)        | 0.999   |
| Access Site                                   |                   |                  |         |
| Transfemoral, n (%)                           | 2127 (81.1)       | 334 (74.4)       | 0.005   |
| Transapical, n (%)                            | 249 (9.49)        | 75 (16.7)        | <0.001  |
| Subclavian, n (%)                             | 85 (3.24)         | 5 (1.11)         | 0.022   |
| Other, n (%)                                  | 160 (6.10)        | 30 (6.68)        | 0.674   |

* Defined as creatinine >200µmol/l or dialysis for renal failure. LVEF: Left Ventricular Ejection Fraction, MI: Myocardial Infarction, NYHA: New York Heart Association, PCI: Percutaneous coronary intervention.
**Supplementary Table 2.** Baseline characteristics across CSHA-estimated frailty groups.

| Variable                                      | CSHA-estimated Frail (n=1043) | CSHA-estimated Non-Frail (n=1581) | p-value   |
|----------------------------------------------|-------------------------------|----------------------------------|-----------|
| Age, mean (SD)                               | 82.0 (7.13)                   | 80.7 (7.82)                      | <0.001    |
| Female, n (%)                                | 525 (50.3)                    | 667 (42.2)                       | <0.001    |
| Diabetic, n (%)                              | 280 (26.8)                    | 361 (22.8)                       | 0.021     |
| Smoker, n (%)                                | 518 (49.7)                    | 798 (50.5)                       | 0.962     |
| Creatinine, mean (SD)                        | 116.5 (67.0)                  | 107.2 (55.6)                     | <0.001    |
| Renal Failure *, n (%)                        | 72 (6.90)                     | 71 (4.49)                        | 0.010     |
| Previous MI, n (%)                           | 246 (23.6)                    | 312 (19.7)                       | 0.021     |
| Pulmonary Disease, n (%)                     | 321 (30.8)                    | 470 (29.7)                       | 0.564     |
| Neurological Disease, n (%)                  | 199 (19.1)                    | 242 (15.3)                       | 0.014     |
| Extracardiac Arteriopathy, n (%)             | 268 (25.7)                    | 287 (18.2)                       | <0.001    |
| Calcification of Ascending Aorta, % (n)       | 116 (11.1)                    | 262 (16.6)                       | <0.001    |
| Atrial Fibrillation, n (%)                   | 296 (28.4)                    | 404 (25.6)                       | 0.138     |
| Previous Cardiac Surgery, n (%)              | 276 (26.5)                    | 523 (33.1)                       | <0.001    |
| Previous PCI, n (%)                          | 201 (19.3)                    | 323 (20.4)                       | 0.501     |
| Height, mean (SD)                            | 1.63 (0.10)                   | 1.65 (0.10)                      | <0.001    |
| Weight, mean (SD)                            | 73.7 (17.5)                   | 75.8 (16.7)                      | 0.003     |
| CCS Class 4, n (%)                           | 12 (1.15)                     | 12 (0.76)                        | 0.412     |
| NYHA ≥ III, n (%)                            | 922 (88.4)                    | 1063 (67.2)                      | <0.001    |
| Aortic Valve Area, mean (SD)                 | 0.68 (0.22)                   | 0.69 (0.24)                      | 0.092     |
| Aortic Valve Peak Gradient, mean (SD)        | 67.4 (26.2)                   | 73.7 (25.9)                      | <0.001    |
| LVEF < 50%, n (%)                             | 416 (39.9)                    | 532 (33.6)                       | 0.001     |
| One or more diseased vessels, n (%)          | 439 (42.1)                    | 619 (39.2)                       | 0.190     |
| Left Main Stem Disease, n (%)                | 56 (5.37)                     | 47 (2.97)                        | 0.002     |
| Non-elective Procedure, n (%)                | 199 (19.1)                    | 166 (10.5)                       | <0.001    |
| Access Site                                  |                               |                                 |           |
| Transfemoral, n (%)                           | 840 (80.5)                    | 1287 (81.4)                      | 0.546     |
| Transapical, n (%)                           | 91 (8.72)                     | 158 (9.99)                       | 0.302     |
| Subclavian, n (%)                             | 34 (3.26)                     | 51 (3.23)                        | 0.999     |
| Other, n (%)                                  | 78 (7.48)                     | 82 (5.19)                        | 0.021     |

* Defined as creatinine >200µmol/l or dialysis for renal failure. LVEF: Left Ventricular Ejection Fraction, MI: Myocardial Infarction, NYHA: New York Heart Association, PCI: Percutaneous coronary intervention.
**Supplementary Table 3.** Baseline characteristics across frailty groups defined with KATZ<6.

| Variable                                      | KATZ<6 (n=846) | KATZ=6 (n=1778) | p-value |
|-----------------------------------------------|----------------|-----------------|---------|
| Age, mean (SD)                                | 81.5 (7.38)    | 81.1 (7.67)     | 0.199   |
| Female, n (%)                                 | 417 (49.3)     | 775 (43.6)      | 0.007   |
| Diabetic, n (%)                               | 217 (25.7)     | 424 (23.8)      | 0.347   |
| Smoker, n (%)                                 | 434 (51.3)     | 882 (49.6)      | 0.252   |
| Creatinine, mean (SD)                         | 113.6 (69.1)   | 109.6 (56.0)    | 0.121   |
| Renal Failure *, n (%)                         | 48 (5.67)      | 95 (5.34)       | 0.783   |
| Previous MI, n (%)                            | 198 (23.4)     | 360 (20.2)      | 0.075   |
| Pulmonary Disease, n (%)                      | 279 (33.0)     | 512 (28.8)      | 0.028   |
| Neurological Disease, n (%)                   | 159 (18.8)     | 282 (15.9)      | 0.069   |
| Extracardiac Arteriopathy, n (%)              | 184 (21.7)     | 371 (20.9)      | 0.635   |
| Calcification of Ascending Aorta, % (n)        | 134 (15.8)     | 244 (13.7)      | 0.167   |
| Atrial Fibrillation, n (%)                    | 263 (31.1)     | 437 (24.6)      | <0.001  |
| Previous Cardiac Surgery, n (%)               | 228 (27.0)     | 571 (32.1)      | 0.009   |
| Previous PCI, n (%)                           | 165 (19.5)     | 359 (20.2)      | 0.725   |
| Height, mean (SD)                             | 1.64 (0.10)    | 1.65 (0.10)     | 0.227   |
| Weight, mean (SD)                             | 75.1 (17.0)    | 74.9 (17.1)     | 0.843   |
| CCS Class 4, n (%)                            | 10 (1.18)      | 14 (0.79)       | 0.439   |
| NYHA ≥ III, n (%)                             | 677 (80.0)     | 1308 (73.6)     | <0.001  |
| Aortic Valve Area, mean (SD)                  | 0.68 (0.23)    | 0.69 (0.23)     | 0.536   |
| Aortic Valve Peak Gradient, mean (SD)         | 70.4 (24.4)    | 71.6 (27.1)     | 0.271   |
| LVEF < 50%, n (%)                             | 356 (42.1)     | 592 (33.3)      | <0.001  |
| One or more diseased vessels, n (%)           | 352 (41.6)     | 706 (39.7)      | 0.416   |
| Left Main Stem Disease, n (%)                 | 36 (4.26)      | 67 (3.77)       | 0.655   |
| Non-elective Procedure, n (%)                 | 161 (19.0)     | 204 (11.5)      | <0.001  |
| Access Site                                   |                |                 |         |
| Transfemoral, n (%)                           | 704 (83.2)     | 1423 (80.0)     | 0.070   |
| Transapical, n (%)                            | 76 (8.98)      | 173 (9.73)      | 0.581   |
| Subclavian, n (%)                             | 22 (2.60)      | 63 (3.54)       | 0.244   |
| Other, n (%)                                  | 44 (5.20)      | 116 (6.52)      | 0.213   |

* Defined as creatinine >200µmol/l or dialysis for renal failure. LVEF: Left Ventricular Ejection Fraction, MI: Myocardial Infarction, NYHA: New York Heart Association, PCI: Percutaneous coronary intervention.
**Supplementary Table 4.** Baseline characteristics across those with/without physician-estimated poor mobility.

| Variable                                      | Poor Mobility (n=591) | Normal Mobility (n=2033) | p-value |
|-----------------------------------------------|-----------------------|--------------------------|---------|
| Age, mean (SD)                                | 81.4 (7.92)           | 81.1 (7.47)              | 0.481   |
| Female, n (%)                                 | 328 (55.5)            | 864 (42.5)               | <0.001  |
| Diabetic, n (%)                               | 151 (25.5)            | 490 (24.1)               | 0.496   |
| Smoker, n (%)                                 | 288 (48.7)            | 1028 (50.6)              | 0.677   |
| Creatinine, mean (SD)                         | 115.3 (80.3)          | 109.6 (53.4)             | 0.045   |
| Renal Failure *, n (%)                        | 42 (7.11)             | 101 (4.97)               | 0.055   |
| Previous MI, n (%)                            | 128 (21.7)            | 430 (21.2)               | 0.844   |
| Pulmonary Disease, n (%)                      | 206 (34.9)            | 585 (28.8)               | 0.004   |
| Neurological Disease, n (%)                   | 112 (19.0)            | 329 (16.2)               | 0.129   |
| Extracardiac Arteriopathy, n (%)              | 165 (27.9)            | 390 (19.2)               | <0.001  |
| Calcification of Ascending Aorta, % (n)       | 91 (15.4)             | 287 (14.1)               | 0.371   |
| Atrial Fibrillation, n (%)                    | 168 (28.4)            | 532 (26.2)               | 0.287   |
| Previous Cardiac Surgery, n (%)               | 131 (22.2)            | 668 (32.9)               | <0.001  |
| Previous PCI, n (%)                           | 93 (15.7)             | 431 (21.2)               | 0.004   |
| Height, mean (SD)                             | 1.63 (0.10)           | 1.65 (0.10)              | <0.001  |
| Weight, mean (SD)                             | 74.8 (17.9)           | 75.0 (16.8)              | 0.818   |
| CCS Class 4, n (%)                            | 7 (1.18)              | 17 (0.84)                | 0.590   |
| NYHA ≥ III, n (%)                             | 489 (82.7)            | 1496 (73.6)              | <0.001  |
| Aortic Valve Area, mean (SD)                  | 0.67 (0.23)           | 0.69 (0.23)              | 0.110   |
| Aortic Valve Peak Gradient, mean (SD)         | 69.3 (25.3)           | 71.8 (26.5)              | 0.050   |
| LVEF < 50%, n (%)                             | 224 (37.9)            | 724 (35.6)               | 0.308   |
| One or more diseased vessels, n (%)           | 231 (39.1)            | 827 (40.7)               | 0.551   |
| Left Main Stem Disease, n (%)                 | 18 (3.05)             | 85 (4.18)                | 0.282   |
| Non-elective Procedure, n (%)                 | 120 (20.3)            | 245 (12.1)               | <0.001  |
| Access Site                                   |                       |                          |         |
| Transfemoral, n (%)                           | 454 (76.8)            | 1673 (82.3)              | 0.004   |
| Transapical, n (%)                            | 80 (13.5)             | 169 (8.31)               | <0.001  |
| Subclavian, n (%)                             | 23 (3.89)             | 62 (3.05)                | 0.374   |
| Other, n (%)                                  | 33 (5.58)             | 127 (6.25)               | 0.623   |

* Defined as creatinine >200µmol/l or dialysis for renal failure. LVEF: Left Ventricular Ejection Fraction, MI: Myocardial Infarction, NYHA: New York Heart Association, PCI: Percutaneous coronary intervention.
**Supplementary Table 5.** Multivariable adjusted short-term outcomes for the sensitivity analysis of the composite frailty indicator. Bold items indicate significant results.

| Composite Frailty       | Moderately frail vs. non-frail multivariable OR (95% CI) * | Severely frail vs. non-frail multivariable OR (95% CI) * |
|-------------------------|------------------------------------------------------------|-------------------------------------------------------|
| 30-day mortality        | 1.19 (0.74, 1.92)                                           | 2.99 (1.71, 5.23)                                      |
| Early Safety            | 1.18 (0.91, 1.52)                                           | 1.88 (1.32, 2.68)                                      |

*: Severely Frail (N=297) corresponds to a patient defined as frail across all three of CSHA, KATZ and poor mobility; Moderately Frail (N=1169) corresponds to a patient that is defined frail by at least one (but not all) of CSHA, KATZ and poor mobility; Non-frail (N=1158) means a patient was defined as not frail by all of CSHA, KATZ and poor mobility.

CI: Confidence Interval, MVC: Major Vascular Complication, OR: Odds Ratio, PPM: Permanent Pacemaker Implantation
Supplementary References

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