Supplementary Material

A Novel UK Prognostic Model for 30-day Mortality following Transcatheter Aortic Valve Implantation

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# Supplementary Methods

## Mathematical Details of Model Updating Techniques

We first derived a logistic regression CPM within the 2009-2014 data, considering only those variables that were observed throughout this period (i.e. not frailty related measures), by following the “majority method” of developing CPMs within multiple imputed data [1]. If $P$ denotes the number of predictors that were selected using the majority method, then one can write the resulting linear predictor (LP) as

$$LP\_{i}=β\_{0}+\sum\_{p=1}^{P}β\_{p}x\_{i,p} (1)$$

for patient $i$, covariates $x\_{i,p}$ for $p\in [1,P]$, and associated estimated coefficients $β\_{p}$.

To ensure the model was reflective of most contemporary practice and to consider the addition of the three frailty measures, we performed model updating on equation (1). Such techniques, as previously described [2–5], have a hierarchical structure to alter a previously fitted CPM, to include potentially new variables. Specifically, we updated equation (1) by fitting a logistic regression model in the 2013-2014 UK TAVI registry with the LP (eq. 1), and the three frailty measures as covariates. Namely, we modelled

$$log\left(\frac{π\_{i}}{1-π\_{i}}\right)=\hat{α}\_{0}+\hat{α}\_{1}LP\_{i}+δ\_{CSHA}x\_{i,CSHA}+δ\_{poor mobility}x\_{i,poor mobility}+δ\_{KATZ}x\_{i,KATZ}$$

where $π\_{i}$ denotes the predicted event probability for patient $i$ in the 2013-14 UK TAVI registry, and $δ$ is the vector of parameters corresponding to each frailty covariate $x$. The parameters $\hat{α}\_{0}$ and $\hat{α}\_{1}$ are the calibration intercept and slope, respectively. The likelihood ratio test was used to determine if any of the three frailty measures significantly improved the fit of the model, with only those meeting this criterion included in the final model; the null model included $\hat{α}\_{0}$ and $\hat{α}\_{1}$ (i.e. we at least applied model recalibration).

## Bootstrapping for in-sample optimism correction

Bootstrap resampling was used to correct the predictive performance of the UK-TAVI CPM for in-sample optimism; the following steps were undertaken:

1. Extract the same random samples (obtained with replacement) from each imputed dataset.
2. Within each sampled imputed dataset, perform exactly the same model selection steps as described in the main paper (i.e. Figure 1). Pool the model coefficients across the bootstrap sampled imputed datasets – call this model the “bootstrap model”.
3. Using the bootstrap model, calculate the “bootstrap apparent performance” within each bootstrap sampled imputed dataset and pool the results using Rubin’s rules.
4. Apply the bootstrap model to the original imputed UK TAVI registry and calculate the performance (pooled across imputations) – call this the “out-of-sample performance”.
5. Calculate the optimism as the difference between the bootstrap apparent performance and the out-of-sample performance.
6. Repeat steps 1-5 another 99 times.
7. Take the mean of the optimism estimates – call this mean the “in-sample optimism”.

The optimism-corrected performance reported within the main paper is then the apparent performance estimates minus the in-sample optimism.

# Supplementary Figures and Tables

**Supplementary Figure 1:** Calibration plot for the finalUK-TAVI CPM. The blue line is a smoother through the observed points and the dashed black line indicates the null hypothesis that the model is perfectly calibrated.



**Supplementary Table 1:** Variable definitions and coding in the UK TAVI registry of all candidate risk factors.

|  |  |  |
| --- | --- | --- |
| **Variable** | **Definition** | **UK TAVI Registry Variable** |
| Mean-centred Age (squared and cubed terms also considered) | Age of the patient at time of procedure minus 81.25 years | Age at Op |
| Female | Female sex | 1.07 Sex |
| Non-Caucasian | Any ethnic origin other than white | 1.08 Ethnic origin |
| Diabetic | Diabetic patient with any of the following treatments: dietary control, insulin, oral medication | 3.01 Diabetes |
| Smoker | Current or ex-smoker | 3.02 Smoking status |
| Mean-centred BMI (squared terms also considered) | The BMI of the patient minus 27.3 | 5.02 Weight and 5.01 Height |
| Glomerular Filtration Rate per 5 unit increase | Calculated by the Modification of Diet in Renal Disease formula, per 5 unit increase \* | Age at Op, 1.07.Sex, 1.08.Ethnic.origin and 3.03 Creatinine |
| Renal Failure | Patient is on dialysis or has a creatinine>200 μmol/L | 3.03 Creatinine and 3.041 On dialysis |
| Recent MI | Any previous MI within 30 days prior to the date of the TAVI operation | 3.05 Previous MI and interval between procedure and last MI |
| Pulmonary disease | Any of the following: (1) Asthma, or (2) COAD /emphysema, or (3) Other significant pulmonary disease | 3.06 History of pulmonary disease |
| Cerebrovascular Disease | Any of the following: (1) CVA with full recovery, or (2) CVA with residual deficit, or (3) TIA or RIND | 3.08 History of neurological disease |
| Extracardiac arteriopathy | Patient has extracardiac arteriopathy | 3.09 Extracardiac arteriopathy |
| Calcified Aorta | Patient has extensive calcification of ascending aorta (grade 3 or 4) | 3.10 Extensive calcification of ascending aorta |
| Sinus Rhythm | Patient has sinus pre-operative rhythm | 3.11 Preoperative heart rhythm |
| Previous Cardiac operation | Any of the following: (1) Previous CABG, or (2) Previous valve operation, or (3) Other operation requiring opening or the pericardium | 4.01 Previous cardiac surgery |
| Prior BAV | Any BAV performed prior (upstream) of the current TAVI procedure | 4.021 Balloon aortic valvuloplasty prior to date of TAVI |
| Previous PCI | Patient had a PCI prior to date of TAVI | 4.03 Previous PCI |
| Critical pre-operative status | Any of the following options: (1) Ventricular tachycardia or fibrillation or aborted sudden death, or (2) Preoperative cardiac massage, or (3) Preoperative ventilation before anaesthetic room, or (4) Preoperative inotropes or IABP, or (5) Preoperative acute renal failure (anuria or oliguria <10ml/hr) | 5.031 Critical preoperative status v4 |
| NYHA class IV | NYHA dyspnoea status recorded as “4. Symptoms at rest or minimal activity” | 5.05 NYHA dyspnoea status (Pre-procedure; stable only) |
| Poor mobility | Poor mobility (Severe impairment of mobility secondary to musculoskeletal or neurological dysfunction) | 3.091 Poor mobility |
| CSHA | CSHA Clinical Frailty Scale score with any option **except**: (1) very fit, or (2) well, or (3) apparently vulnerable | 5.051 CSHA Clinical Frailty Scale score |
| KATZ (per point drop from 6 points) | Katz Index of Independence in Activities of Daily Living, number of points less than 6 (e.g. observed KATZ of 2 points becomes 4 after the transformation) | 6 points - 5.052 Katz Index of Independence in Activities of Daily Living |
| PA Systolic pressure >60mmHg | PA systolic > 60mmHg | 6.012 PA systolic pressure (mmHg) |
| Aortic peak gradient | Aortic valve peak gradient (mmHg) | 6.02 Aortic valve peak gradient |
| Aortic valve area per 0.1 unit increase | Aortic valve area for every 0.1 cm2 increase | 6.03 Aortic valve area |
| LVEF <50% | Left ventricular ejection fraction less than 50% | 6.08 LV function |
| More than one diseased vessel | Extent of coronary vessel disease (ignoring LMS disease) with any option **other than** “no vessel with >50% diameter stenosis” | 6.09 Extent of coronary vessel disease |
| Left main stem disease | Left main stem disease with >50% diameter stenosis | 6.10 Left main stem disease |
| Non-elective procedure | Any procedure that was (1) urgent, or (2) emergency, or (3) salvage | 7.06 Procedure urgency |
| Non-transfemoral access | Any access route **other than** Femoral (percutaneous) or Femoral (surgical) | 7.10 Delivery approach |

\*: GFR (mL/min/1.73 m2) = 175 x (Serum creatinine [mg/dL])-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if ethnic origin recorded as “other” in UK TAVI registry)

**Supplementary Table 2:** Apparent model performance across empirical quantiles of predicted risk from the UK-TAVI CPM.

|  |  |  |  |
| --- | --- | --- | --- |
| **Quartile (predicted risk range)** | **Calibration Intercept (95% CI)** | **Calibration Slope (95% CI)** | **AUC (95% CI)** |
| 1st (0% - 2.07%) | 0.04 (-0.54, 0.62) | 2.33 (-1.39, 6.05) | 0.60 (0.45, 0.75) |
| 2nd (2.07% - 2.89%) | -0.13 (-0.65, 0.39) | 4.32 (-1.05, 9.69) | 0.63 (0.50, 0.77) |
| 3rd (2.98% - 4.84%) | 0.18 (-0.20, 0.55) | 0.90 (-1.65, 3.45) | 0.54 (0.44, 0.64) |
| 4th (4.84% - 44.4%) | -0.06 (-0.33, 0.21) | 1.12 (0.60, 1.65) | 0.66 (0.59, 0.74) |

**Supplementary Table 3:** Bootstrap corrected model performance for the UK-TAVI CPM across different patient subgroups.

|  |  |  |  |
| --- | --- | --- | --- |
| **Subgroup** | **Calibration Intercept (95% CI)** | **Calibration Slope (95% CI)** | **AUC (95% CI)** |
| Age |  |  |  |
|  <85 years | 0.06 (-0.18, 0.29) | 0.86 (0.57, 1.15) | 0.68 (0.62, 0.74) |
|  ≥85 years | -0.04 (-0.34, 0.25) | 0.64 (0.22, 1.06) | 0.61 (0.53, 0.70) |
| Sex |  |  |  |
|  Male | 0.06 (-0.20, 0.31) | 0.92 (0.59, 1.24) | 0.68 (0.61, 0.75) |
|  Female | -0.03 (-0.29, 0.24) | 0.65 (0.30, 1.01) | 0.63 (0.56, 0.70) |
| Renal Failure |  |  |  |
|  Yes | 0.01 (-0.64, 0.67) | 0.82 (0.01, 1.64) | 0.66 (0.46, 0.86) |
|  No | 0.02 (-0.17, 0.21) | 0.78 (0.53, 1.04) | 0.66 (0.61, 0.71) |
| Previous Cardiac Surgery |  |  |  |
|  Yes | 0.18 (-0.15, 0.50) | 0.63 (0.23, 1.02) | 0.66 (0.57, 0.74) |
|  No | -0.05 (-0.28, 0.17) | 0.89 (0.59, 1.19) | 0.66 (0.60, 0.72) |
| NYHA |  |  |  |
|  Class IV | 0.19 (-0.18, 0.56) | 0.78 (0.35, 1.21) | 0.69 (0.60, 0.79) |
|  Class I – III | -0.04 (-0.25, 0.18) | 0.74 (0.44, 1.04) | 0.64 (0.58, 0.69) |
| LVEF |  |  |  |
|  <50% | 0.09 (-0.18, 0.37) | 1.13 (0.77, 1.49) | 0.75 (0.69, 0.81) |
|  ≥50% | -0.04 (-0.29, 0.21) | 0.44 (0.09, 0.79) | 0.58 (0.51, 0.65) |
| Frailty |  |  |  |
|  KATZ=6 | -0.03 (-0.30, 0.24) | 0.54 (0.04, 1.05) | 0.57 (0.50, 0.65) |
|  KATZ<6 | 0.06 (-0.20, 0.32) | 0.85 (0.48, 1.22) | 0.67 (0.61, 0.73) |
|  Poor Mobility | 0.02 (-0.27, 0.30) | 0.76 (0.29, 1.22) | 0.62 (0.54, 0.70) |
|  Normal Mobility | 0.02 (-0.22, 0.26) | 0.81 (0.39, 1.24) | 0.62 (0.56, 0.69) |
| Access route |  |  |  |
|  Transfemoral | 0.03 (-0.19, 0.25) | 0.90 (0.61, 1.19) | 0.66 (0.60, 0.72) |
|  Non-Transfemoral | -0.02 (-0.36, 0.32) | 0.50 (-0.02, 1.01) | 0.58 (0.48, 0.68) |
| Valve type |  |  |  |
|  SAPIEN | 0.07 (-0.16, 0.30) | 0.66 (0.36, 0.97) | 0.64 (0.57, 0.70) |
|  CoreValve | 0.06 (-0.26, 0.37) | 0.97 (0.57, 1.38) | 0.69 (0.62, 0.77) |

**Supplementary Table 4:** Variables included in the model within the sensitivity analysis that only singularly imputed missing data.

|  |  |  |
| --- | --- | --- |
| **Variable \*** | **Coefficient (SE)** | **OR (95% CI)** |
| Intercept | -3.3855 (0.2432) | N/A |
| Mean-centred Age | 0.0131 (0.0085) | 1.0132 (0.9965, 1.0302) |
| Female | 0.1605 (0.1185) | 1.1741 (0.9308, 1.4810) |
| Mean-centred BMI | -0.0267 (0.0118) | 0.9736 (0.9514, 0.9964) |
| Mean-centred BMI squared | 0.0011 (0.0000) | 1.0011 (0.9998, 1.0024) |
| Glomerular Filtration Rate per 5 unit increase | -0.0346 (0.014) | 0.966 (0.9398, 0.9929) |
| Pulmonary disease | 0.2103 (0.1253) | 1.2340 (0.9653, 1.5776) |
| Extracardiac arteriopathy | 0.1837 (0.1350) | 1.2016 (0.9222, 1.5657) |
| Calcified Aorta | 0.1785 (0.1430) | 1.1955 (0.9032, 1.5823) |
| Sinus pre-operative heart rhythm | -0.1522 (0.1197) | 0.8588 (0.6792, 1.0860) |
| Prior BAV | 0.2742 (0.1636) | 1.3155 (0.9547, 1.8128) |
| Critical pre-operative status | 0.6772 (0.3129) | 1.9684 (1.066, 3.6347) |
| Poor Mobility | 0.6713 (0.2023) | 1.9567 (1.3161, 2.9092) |
| KATZ (per point drop from 6 points) | 0.2053 (0.0679) | 1.2279 (1.0749, 1.4028) |
| PA Systolic pressure >60mmHg | 0.2884 (0.1604) | 1.3343 (0.9743, 1.8273) |
| Aortic peak gradient | -0.0032 (0.0023) | 0.9968 (0.9923, 1.0014) |
| Non-elective procedure | 0.3740 (0.1575) | 1.4536 (1.0675, 1.9793) |
| Non-transfemoral access | 0.5699 (0.1265) | 1.7682 (1.3798, 2.2659) |

*Abbreviations: BAV: Balloon aortic valvuloplasty, BMI: Body mass index, OR: Odds ratio, SE: standard error*

*\*: Variable definitions are given in Supplementary Table 1.*

**Supplementary Table 5:** Variables included in the model within the sensitivity analysis that limited the development cohort to those procedures between January 2013 and December 2014.

|  |  |  |
| --- | --- | --- |
| **Variable \*** | **Coefficient (SE)** | **OR (95% CI)** |
| Intercept | -3.1635 (0.3166) | N/A |
| Mean-centred Age | 0.0069 (0.0134) | 1.0070 (0.9810, 1.0337) |
| Female | 0.0292 (0.1904) | 1.0297 (0.7090, 1.4953) |
| Diabetes | -0.4040 (0.2538) | 0.6676 (0.4060, 1.0980) |
| Mean-centred BMI | -0.0294 (0.0184) | 0.9710 (0.9367, 1.0066) |
| Glomerular Filtration Rate per 5 unit increase | -0.0492 (0.0221) | 0.9520 (0.9116, 0.9941) |
| Pulmonary disease | 0.3507 (0.1991) | 1.4201 (0.9613, 2.0979) |
| Sinus pre-operative heart rhythm | -0.3001 (0.1932) | 0.7407 (0.5072, 1.0817) |
| NYHA Class IV | 0.4559 (0.2213) | 1.5775 (1.0224, 2.4340) |
| Poor Mobility | 0.6496 (0.2067) | 1.9148 (1.2769, 2.8715) |
| KATZ (per point drop from 6 points) | 0.2550 (0.0687) | 1.2904 (1.1279, 1.4763) |
| Non-transfemoral access | 0.5557 (0.2103) | 1.7431 (1.1544, 2.6322) |

*Abbreviations: BAV: Balloon aortic valvuloplasty, BMI: Body mass index, NYHA: New York Heart Association Functional Classification, OR: Odds ratio, SE: standard error*

*\*: Variable definitions are given in Supplementary Table 1.*

# Supplementary References

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