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13 **Article title:** Identification of clinical factors predicting warfarin sensitivity
14 after cardiac surgery

15

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29

30 **Abstract**

31

32 **Objectives:** Warfarin is commonly initiated post-cardiac surgery to reduce the risk of
33 intra-cardiac thrombus formation. Studies have found that sensitivity is increased
34 after cardiac surgery and anti-coagulation is subsequently difficult to manage. This
35 study set out to identify clinical markers of increased warfarin sensitivity in
36 patients' post-cardiac surgery, and build a model that can predict warfarin
37 sensitivity, and improve safety in this setting. **Methods:** The study was an
38 observational, retrospective cohort design. Clinical parameters including Left
39 Ventricular Ejection Fraction (LVEF), cross-clamp time, age, serum albumin and C-
40 reactive protein concentrations were collected from consenting patients who had
41 undergone cardiac surgery and prescribed post-operative warfarin. Warfarin Dose Index
42 (WDI) was calculated for each patient from their INR and warfarin dose, as a measure
43 of sensitivity. **Results:** 41 patients were recruited to the study. Logarithmically
44 transformed WDI (log WDI) significantly correlated with LVEF, cardiopulmonary bypass
45 (CPB) time, cross-clamp time, baseline INR and co-administration of amiodarone
46 ($p < 0.05$). When added to a linear regression model, LVEF and cross-clamp time produced
47 a model that accounted for 41% of variance in log WDI ($R^2 = 0.41$), $p = 0.0002$). Applying
48 a log WDI cut-off value of -0.349 discriminated between patients who develop an INR
49 > 4 and those who do not with a sensitivity of 75% and a specificity of 70%.
50 **Conclusions:** This single centre study has highlighted two risk factors for increased
51 warfarin sensitivity post-cardiac surgery. Further research is needed to confirm
52 these findings in a wider, more diverse population, and to validate this model.

53

54 **Keywords:** Warfarin; anticoagulation; anticoagulants; risk-prediction; adverse drug
55 reactions; cardio-thoracic surgery; surgery

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58

59 **1. Introduction**

60 Warfarin is an anticoagulant medication used for the treatment and prevention of
61 thromboembolic disorders such as deep vein thrombosis and pulmonary embolism [1]. It
62 inhibits the enzyme Vitamin K Epoxide Reductase (VKOR), blocking the formation of
63 reduced vitamin K, which is necessary for the synthesis of the clotting factors II,
64 VII, IX, X, and of the anticoagulants protein C and protein S [2]. There is wide
65 inter-patient variability in the response to warfarin, and as a consequence dosing
66 needs to be tailored to individual patients. Factors that are known to affect warfarin
67 response include diet, co-administration of interacting drugs and single nucleotide
68 polymorphisms for the genes that code Cytochrome P450 isoenzyme CYP2C9 and VKOR [1].

69
70 Another factor which is increasingly recognised as affecting the sensitivity to
71 warfarin is a recent history of cardiac valve surgery. Studies have found that in
72 the initial post-operative period following valve replacement, certain patients show
73 an exaggerated response to warfarin when compared to non-surgical patients [3-5].
74 The sensitivity appears to be prolonged, and can lead to poor control in the 3-month
75 period after valve replacement [6]. However, after this period, sensitivity is
76 thought to return to normal. There is therefore a critical window for potential harm,
77 especially during period of warfarin loading. There is variation in this population
78 however, and whilst some patients show increased sensitivity to warfarin, others do
79 not. A universal, bespoke dosage regimen in this population may therefore be
80 inappropriate.

81
82 Theories for the increased sensitivity include myocardial dysfunction and fluid
83 overload during surgery, which has been hypothesized to lead to hepatic congestion
84 which then may affect warfarin metabolism or the synthesis of clotting factors [3-
85 7]. As warfarin is 99% bound to plasma proteins (mainly albumin), hypoalbuminemia,
86 caused by an inflammatory response or haemodilution as a consequence of
87 cardiopulmonary bypass (CPB), may also be implicated [3-4,8]. Interacting drugs

88 commonly used after cardiac surgery are also expected to influence sensitivity [9,
89 14-15]. In studies looking at factors influencing sensitivity in this patient group,
90 baseline INR, serum albumin, amiodarone and antimicrobial prophylaxis have been
91 identified as risk factors [3, 9-11].

92
93 Despite studies finding increased sensitivity in patients after cardiac valve surgery,
94 and the identification of various factors that may contribute to altered response,
95 guidance on dosing in this patient group remains limited, and, as a consequence,
96 anticoagulation is poorly managed. A recent study by Roberts et al investigated the
97 implementation of a warfarin dosing protocol post-valve surgery, suggesting a 30%
98 reduction in warfarin doses in all patients. However, this strategy, whilst reducing
99 the risk of bleeding complications, may leave some non-sensitive patients under-
100 anticoagulated, and at risk of thrombus formation [12]. Another study by Meijer et
101 al developed a specific dosing algorithm post valve-surgery. Despite improving the
102 individual time in therapeutic range, patients in the algorithm group spent more time
103 with a supra-therapeutic INR compared with the non-algorithm group [13]. Identifying
104 clinical and biochemical markers that are associated with increased postoperative
105 sensitivity, and then incorporating them into a risk prediction tool could therefore
106 aid the personalization of dosing in this setting and minimize the risk of over-
107 anticoagulation and the associated risk of bleeding.

108
109 The published evidence of increased sensitivity is currently limited to patients that
110 have undergone cardiac valve surgery, however, many of the hypotheses to explain the
111 increased sensitivity are pertinent to patients undergoing other types of cardiac
112 surgery, for example, coronary artery bypass graft. Here, damage to the myocardium
113 as a result of ischaemia during aortic clamp may lead to an acute deterioration in
114 left ventricular function, and hepatic congestion, and altered sensitivity to
115 warfarin. The purpose of the current study was therefore to identify clinical and
116 biochemical markers of increased warfarin sensitivity in patients that have undergone

117 a range of cardiac surgeries, and to build a model that could, after validation, be
118 used to predict the risk of warfarin sensitivity in the immediate post-operative
119 period. The model could also be used to provide guidance on warfarin dosing.

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127 **2. Methods**

128 The study was a non-interventional, retrospective cohort study. It received approval
129 from the National Health Service Research Ethics Service (REC approval number:
130 15/EE/0082). Data were collected as a convenience sample, between April 2015 and
131 September 2015, from consenting patients.

132

133 *2.1 Inclusion criteria*

- 134 1. Inpatient admission following cardiac surgery (not limited to valve
135 repair/replacement)
- 136 2. Prescribed postoperative warfarin
- 137 3. Over 18 years
- 138 4. Capacity to consent as determined by the patients' ability to retain and understand
139 the information given on the patient information sheet

140

141 *2.2 Exclusion Criteria*

- 142 1. Acute or chronic liver failure as determined from the patient's medical history
143 and preoperative liver function tests
- 144 2. Baseline INR >1.5

145

146 *2.3 Data collection*

147 Participants were given a Patient Information Sheet (PIS) prior to surgery and
148 enrolled in the study towards the end of their inpatient stay after they had recovered.
149 The following data were then collected for each participant: demographics, type of
150 surgery, cardio-pulmonary bypass (CPB) time, cross clamp-time, urea and electrolytes
151 (U&Es), C-reactive protein (CRP), liver function tests (LFTs), International
152 Normalised Ratio (INR), left ventricular ejection fraction (LVEF), concurrent
153 medication prescribed, medication history, warfarin dose, indication and target INR.
154 Warfarin dose index (WDI) was used as an outcome measure for warfarin sensitivity
155 (Equation 1, [11]). The WDI is a well-established measure of sensitivity during both

156 warfarin initiation, and maintenance stages. The index normalizes the patient's
157 clotting time (international normalized ratio [INR]) at day 4 following commencement
158 of warfarin loading, to dose mean dose over the preceding 3 days.

159

160 **Equation 1:** $WDI = \text{INR (day 4*)} / \text{mean warfarin dose for preceding 3 days}$

161 * Post warfarin loading

162

163 *2.4 Statistical power calculation*

164 Sample size was calculated using the 'pwr' package in R (v3.2.1). For a final linear
165 regression model with between 3-5 predictor variables, a sample of 35-42 patients is
166 required to detect a large effect ($F^2=0.35$) with $\alpha=0.05$ and $\beta-1=0.80$. For the same
167 number of predictors (3-5) and an $F^2=0.15$ (medium effect) a sample size of 77-91
168 patients is required. We anticipated that our predictors would have a medium to large
169 effect and so our target sample size was set to 35-50.

170

171 *2.5 Statistical model*

172 We built a linear regression model using the \log_{10} of the WDI (log WDI) as our dependent
173 variable, and factors hypothesized to alter warfarin sensitivity as our predictor
174 variables. To determine which of the predictor variables collected should be included
175 in our first iteration of the model we performed a series of correlations between
176 these variables and log WDI. A Pearson Correlation was used for continuous variables
177 that 1) demonstrate a normal distribution and 2) have no significant outliers [14-
178 15]. For variables with a significant ($p<0.05$) Shapiro-Wilk test, or where there are
179 extreme outliers in the sample, a Spearman Rank test was performed [15, 17]. For
180 dichotomous predictor variables a Point-Biserial Correlation was performed after
181 assessing normality and homogeneity of variance [14, 17]. Correlation coefficients
182 are reported as r (Pearson's), ρ (Spearman's) and ρ_{pb} (Pearson's Point Biseral).
183 Variables with a p value of ≤ 0.15 were then added to a linear regression model with

184 log WDI as the dependent variable. A significance level of $p < 0.05$ was accepted as
185 statistically significant.

186

187 In describing continuous data with a normal distribution, mean \pm standard deviations
188 were used. For continuous data that was not normally distributed the median and
189 interquartile ranges (IQR) is presented. Our final model was tested for the following
190 assumptions of linear regression: independence of errors, collinearity, normal
191 distribution of errors, linearity and heteroscedascity [13-21]. The British Society
192 of Echocardiography Guidelines were used to categorise LVEF into groups [22].

193

194 Receiver operating characteristics curves, area under the receiver operator curves
195 (AUROC), and sensitivity and specificity values were calculated using Graphpad Prism
196 6.0. Youden's index was calculated as: $(\text{sensitivity} + \text{specificity}) - 1$. The AUROC and
197 Youden's index were used to determine an appropriate cut-off value for log WDI to
198 predict INR >4 during inpatient stay with maximum sensitivity and specificity.

199

200 Data analysis was conducted with SPSS version 22.0, Graphpad Prism 6.0, and R.

201

202

203 3. Results

204

205 Out of 55 patients admitted for cardiac surgery and initiated on warfarin during the
206 study period, 41 patients were eligible for inclusion in the study. 35 of these
207 patients had a complete dataset and were included in the final model (Figure 1). A
208 breakdown of baseline demographic details is found in Table 1. Patients received
209 post-operative warfarin for a range of indications including atrial fibrillation,
210 mechanical mitral valve replacement, and mitral valve repair (Table 2). Of the 35
211 patients included in the final model, 31 were admitted for valve related surgery, and
212 4 for non-valve related surgery. Non-valve related surgery included coronary artery
213 bypass graft (CABG), atrial ablation, and surgical treatment of atrial myxoma and
214 left atrial appendage occlusion.

215

216 3.1 Dosing and INR Ranges

217 Warfarin was started a median of 1 day after surgery (IQR = 1 - 3, range 0 - 18 days)
218 and took a median of 5 days to reach the therapeutic range (IQR 4 - 7 days, range 3
219 - 21 days). Over the first 3 days of loading a median dose of 4 mg daily was used
220 (IQR 3 - 5 mg). The median cumulative dose to achieve therapeutic range was 20 mg,
221 (IQR 13.0 - 27.5 mg).

222

223 Fifteen (37%) patients had an INR value which exceeded the patient's target
224 therapeutic range for a median of 2.5 days (IQR 2 - 4.5 days, range 1 - 6 days) and
225 of these, 12 (80%) patients had an INR > 4.0. One patient had vitamin K administered
226 to reverse an INR of 7.5. During the study 10 (24%) patients had a total of 39 doses
227 omitted due to the INR exceeding the therapeutic range. Discharge was delayed in
228 four patients (10%) due to the INR being below the therapeutic range and one patient
229 had a delayed discharge due to the INR being too high. Comparing valve and non-valve
230 related surgery patients, 9/31 in the valve related surgery group, and 3/4 in the

231 non-valve related surgery group developed and INR >4 during loading with warfarin
232 post-surgery.

233

234 3.2 Bivariate Correlation

235 To identify variables to enter in the first iteration of our model we performed a
236 series of statistical correlation tests between log WDI and predictor variables
237 (supplementary material). From these correlations we identified left ventricular
238 ejection fraction (LVEF), CPB, cross-clamp time, baseline INR, and the co-
239 administration of amiodarone and omeprazole as potential predictors. Other factors
240 that have previously been associated with warfarin sensitivity, such as age, gender
241 and weight were not significantly correlated with log WDI in this sample ($\rho=0.019$,
242 $p=0.907$ age; $r_{pb}=0.056$, $p=0.728$ gender; $r=-0.068$, $p=0.676$ weight) and therefore were
243 not included in the model.

244

245 3.3 Linear regression

246 Initially the predictors identified were added to the linear regression model as
247 single variables. As single predictors of sensitivity LVEF, cross clamp-time, CPB
248 time and the addition of amiodarone (n=20/41) all had statistically significant
249 changes in the F-ratio, $F(1,33) = 15.87$, $p = 0.00035$, $F(1,39) = 4.817$, $p = 0.034$,
250 $F(1,39) = 4.665$, $p = 0.037$ and $F(1,39) = 4.743$, $p = 0.036$ respectively. As a single
251 predictor LVEF accounted for 32.5% of variability in the model ($R^2 = 0.325$, adjusted
252 $R^2 = 0.304$, n=35, Figure 2) and when combined with cross-clamp time the model accounted
253 for 41% of the variance ($R^2 = 0.41$, adjusted $R^2 = 0.373$, n=35). The combination of
254 LVEF and length of cross-clamp time provided the best fit of the data (Table 3). The
255 addition of amiodarone (F change = 1.307, $p = 0.261$), or CPB time (F change = 2.858,
256 $p = 0.101$) to LVEF did not significantly improve the model. The equation for our
257 final model is shown in equation 2, in which $E[\text{LogWDI}_i]$ is the expected values of
258 LogWDI_i .

259

260 **Equation 2:** $E[\text{LogWDI}_i] = 0.026 + (-0.011 \times \text{LVEF}_i) + (0.002 \times \text{clamptime}_i)$.

261

262 *3.4 Model Assumptions*

263 Independence of residuals was confirmed with a Durban Watson test = 2.607. There was
264 a small correlation between LVEF and cross-clamp time ($r = .130$) but assessment of
265 collinearity was acceptable ($\text{VIF} = 1.017$). There was a normal distribution of the
266 residuals as confirmed with a frequency histogram and a P-P plot. From visual
267 inspection of a plot of standardised predicted values against standardised residuals
268 there was no evidence of non-linearity or heteroscedascity. To detect outliers, the
269 standardised residuals were set at ± 3 ($z\text{-score} = 2.56$), which all were below this
270 range. The leverage value calculated was 0.086 and 2 cases had values greater than
271 twice this value but the Cooks distances conformed to the accepted criteria so none
272 of the data points would exert a high influence over the regression line.

273

274 *3.5 Clinical Predictors*

275 Left Ventricular Ejection Fraction (LVEF): 18 (51%) patients had good LVEF, 12 (34%)
276 mild LVEF, 2 (6%) moderate LVEF and 3 (9%) poor LVEF. Log WDI was statistically
277 significantly different amongst the groups ($p = 0.033$, $n=35$, Kruskal-Wallis).

278

279 *3.6 Using the model to predict patients who develop INR >4 during stay*

280 Using a patient's LVEF and cross-clamp time to predict log WDI may be of benefit to
281 clinicians who are initiating warfarin, as it could, for example, be used to calculate
282 the mean daily loading dose required to reach a target INR by day 4. This may not
283 however be practical in a busy ward situation, and may introduce a focal point for
284 medication error due to the multi-step nature of the calculation required to determine
285 a loading dose. It may therefore be more useful to use the model to categorise
286 patients as either high-risk, or low-risk; those individuals deemed high risk should
287 then be loaded more cautiously with warfarin. To use the model in this way, we must
288 first identify a 'cut-off' value in the 'predicted' log WDI above which there is high

289 sensitivity and specificity for detecting high-risk individuals. High-risk
290 individuals in this case were considered those patients' who had developed an INR ≥ 4
291 during their inpatient stay. From our dataset we categorised patients according to
292 whether they had developed an INR ≥ 4 , and then calculated their 'predicted' log WDI
293 using equation 2. This allowed us to construct a Receiver Operating Characteristics
294 (ROC) curve to determine an appropriate cut-off value (Figure 3).

295

296 From our study, 12/35 patients had an INR of ≥ 4 during their inpatient stay. We
297 identified a predicted log WDI cut-off value of -0.380 from our ROC curve (area under
298 ROC = 0.7 (0.5-0.9), Figure 2). Using this cut-off value, we correctly identified,
299 retrospectively, 9/12 patients who went on to develop a peak INR > 4 during their
300 inpatient stay (sensitivity 75%), and 17/23 patients with a peak INR < 4 during
301 inpatient stay (specificity 70%). Youden's index, which is a measure of the accuracy
302 of our model, was calculated as $J=0.45$, and the positive predictor, and negative
303 predictor values as 56% and 85% respectively.

304

305

306

307 **4 Discussion**

308

309 This study aimed to build a model to predict warfarin sensitivity in patients
310 undergoing cardiothoracic surgery, using a range of routinely available clinical
311 variables. In doing so we discovered that compromised cardiac function and the time
312 spent on clamp increased the risk of developing sensitivity to warfarin post-surgery.

313

314 During the study, 37% of patients exceeded their target INR range. Of these, 29% had
315 an INR > 4.0. For this population, these results are comparable with other studies
316 looking at warfarin response after cardiac surgery, where between 38% and 48.8% of
317 patients exceeded the therapeutic range [3, 5] and 25% patients had an INR ≥4.0 in
318 the induction period [4]. Whilst there is no current guideline for dosing patients
319 after surgery in the UK, the range of dosing used was consistent for the majority of
320 patients over the first 3 days of loading, with a median of 4 mg daily (IQR 3 - 5
321 mg). Whilst other studies have suggested dosing all patients at lower doses [7], or
322 applying a dosing algorithm to reduce the risk of high INRs during this period, this
323 could result in delayed discharges due to sub therapeutic INRs. Therefore, a targeted,
324 individualized approach to dosing would be advantageous, in terms of the patient
325 experience, safety, and healthcare associated costs.

326

327 Of the factors hypothesized to be associated with increasing warfarin sensitivity,
328 LVEF had a large effect size ($r=0.57$) and a statistically significant negative
329 correlation associated with increased response to warfarin. CPB time, amiodarone and
330 baseline INR were also found to have statistically significant positive correlations
331 with the outcome measure, all with medium effect sizes. However, when added to our
332 regression model, they did not increase the explanatory power of LVEF in predicting
333 warfarin sensitivity. This study was not powered to assess this further.

334

335 4.1 Heart Failure

336 The negative relationship between LVEF and warfarin sensitivity is perhaps
337 counterintuitive: warfarin is a low extraction drug, and elimination is not considered
338 to be dependent upon hepatic blood flow [23], which is compromised in heart failure
339 (a low LVEF). However, there are reports of an association between heart failure and
340 increased response to warfarin in the literature, although some of these studies are
341 older and problematic. For example, some used prothrombin time rather than INR [24]
342 as a measure of warfarin efficacy, the parameters of which can vary between
343 laboratories.

344

345 There are also conflicting findings between whether dose requirements are altered
346 because of decompensated heart failure, or if the effect also manifests for stable
347 heart failure [24]. A small study (n = 63) looking for factors affecting the
348 maintenance dose in Hong Kong Chinese patients, found that chronic heart failure (n
349 = 6) negatively correlated with warfarin dosage requirement ($r = -0.26$, $p = 0.025$)
350 [25]. Doecke et al. (1991) also found that stable chronic heart failure was associated
351 with increased response to warfarin during initiation [26].

352

353 Del Campo et al (2015) found warfarin sensitivity (WDI) to be significantly increased
354 during exacerbations of heart failure and chronic obstructive pulmonary disease (COPD)
355 when compared to a periods of disease stability [27]. The heart failure group had
356 significantly greater sensitivity at admission compared to the COPD and control groups
357 but no difference in sensitivity between the groups during periods of disease
358 stability. This would indicate a transient change, relating to the exacerbation,
359 which supports the theory relating to increased sensitivity for decompensated disease.
360 Significantly more patients presented with $INR \geq 4$ in NYHA class 3 and 4 compared to
361 NYHA class 1 and 2 (41% vs. 7% respectively $p = 0.028$), indicating increased
362 sensitivity with worsening function as found in this study.

363

364 Theories relating to proposed mechanisms for increased response in heart failure
365 exacerbations relate to either the pharmacodynamic effect on clotting factor
366 synthesis, or proposed pharmacokinetic mechanisms of reduced warfarin metabolism or
367 clearance. As the liver is the site of synthesis for vitamin K dependent clotting
368 factors, a decrease in synthesis due to hepatic congestion has been suggested [24].

369

370 *4.2 Cardiopulmonary Bypass Time, Cross-clamp Time and Warfarin Sensitivity*

371 Cardiopulmonary bypass is the use of an extracorporeal circuit to maintain circulation
372 to the body during cardiothoracic surgery [28]. A cross-clamp is placed across the
373 aorta to isolate the coronary circulation and can, in some circumstances lead to
374 hypoxic damage of the myocardium, although various techniques are used to mitigate
375 this [28]. Increasing length of cross-clamp time and CPB time were both found to be
376 significantly correlated with increasing warfarin sensitivity and may be related to
377 ensuing damage. However, other studies in this patient group did not find any
378 relationship between CPB times in either of their cohorts when looking at warfarin
379 sensitivity [11, 14], but may be related to differences in surgical procedures or
380 patient demographics.

381

382 Both prolonged CPB and cross-clamp time are associated with increased morbidity and
383 mortality following cardio-thoracic surgery. There is evidence that during the period
384 of the cross-clamp, myocardial ischemia induces a systemic inflammatory response
385 syndrome (SIRS) [29]. Pro-inflammatory cytokines, including interleukin 6 (IL-6),
386 tumour necrosis factor α (TNF- α), interleukin 1 (IL-1) and endotoxin are released as
387 part of the SIRS response, thought to result from the exposure of blood to the
388 artificial surface of the bypass circuit [29-30]. Cytokines, such as IL-1, IL-6, TNF
389 α and interferon have all been shown to have an effect on drug metabolism [31].
390 Production of cytokines, which may be responsible for the down regulation of
391 individual CYP450 isoforms has been proposed as a mechanism for significant decreases
392 in CYP450 related drug metabolism in critically ill patients with SIRS [32-33]. Peak

393 CRP was investigated in this study as a marker of inflammation but did not
394 significantly correlate with log WDI, having a small effect size. As IL-6 seems to
395 be implicated in both drug metabolism and the systemic inflammatory response from CPB
396 this would appear to be a more useful indicator of this effect and worth investigating
397 in the future.

398

399 *4.3 Amiodarone*

400 Amiodarone was the only interacting drug which correlated with warfarin sensitivity
401 in this study, however, it failed to reach significance when included in our model.
402 One possible reason for this could be the temporal trajectory over which the
403 interaction occurs. If we were to conduct the study over a longer period for example,
404 we may find this predictor plays a more prominent role in our model.

405

406 *4.4 Limitations*

407 A patient's response to warfarin therapy can be affected by various factors, including
408 diet (vitamin K intake), genotype, and co-prescribed interacting drugs. Whilst we
409 included major interacting drugs in our model, we did not collect data on genotype,
410 or diet. Doing so may have improved our model. However, with respect to genotype,
411 this is a factor which is not routinely screened for in the UK, and its inclusion in
412 this model may have meant that using it as a risk prediction, or dosing tool would
413 not be practical.

414

415 One further limitation includes the small sample size, and use of a single site for
416 recruitment. Despite the small numbers of patients, our study was powered to identify
417 predictor variables that had a medium, and hence clinically important effect size.
418 Nevertheless, further research is required to confirm these preliminary findings, and
419 validate our model in a more diverse patient population.

420

421

422 **5. Conclusion**

423

424 In this study, we found that 37% of patients had an INR above their therapeutic range
425 and 29% had an INR ≥ 4.0 , which can lead to patient harm and delay discharge from
426 hospital. We identified two clinical markers that contributed to increased
427 postoperative sensitivity to warfarin in patients that had undergone a range of valve
428 related and non-valve related cardiac surgery. These were LVEF and length of cross-
429 clamp time. By adding these to a linear regression model, they accounted for 41% of
430 the variance in response to warfarin in the initial loading period in this cohort.
431 Application of a log WDI cut-off value of -0.380 was able to successfully identify
432 75% of patients with and INR ≥ 4 . It should be noted however that this is a single
433 centre study, and further research is required to confirm these findings in a more
434 diverse patient population, and rule out the influence of confounders. But, once
435 validated, our model could be used to predict patients that are sensitive to warfarin
436 following cardiothoracic surgery, and provide guidance of a suitable loading dose to
437 achieve a target INR. This could reduce the risk of over anticoagulation in the early
438 postoperative stages and lead to significant improvements in the dosing of this
439 population.

440

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443

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447

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449

450 **Declaration of interest**

451 We confirm that there are no actual or potential conflicts of financial interest with
452 any of the authors, or the authors' respective institutions.

453

454

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456

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555 (9), 449-462;2008

556 Figure 1. Differences between warfarin sensitivity (log WDI) and categories of left
557 ventricular ejection fraction (LVEF) for patients undergoing cardiothoracic surgery
558 and participating in the study (n = 41). The category of LVEF was assigned according
559 to the British Society of Echocardiography Guidelines [19]: Good = $\geq 55\%$, mild = 45
560 - 54%, moderate = 36 - 44% and poor = $\leq 35\%$. Outliers are denoted by circular dots,
561 indicating 1.5 times the box length and extreme outliers are denoted by * indicating
562 3 times the box length. Kruskal-Wallis test, * p < 0.05.

563

564 Figure 2. Scatter plots demonstrating the relationship between the two variables:
565 Left Ventricular Ejection Fraction (LVEF, $R^2=0.32$, $p<0.001$) and Cross Clamp Time
566 ($R^2=0.013$, $p<0.05$), and warfarin sensitivity (logWDI).

567

568 Figure 3. Receiver operating characteristics (ROC) curve showing the sensitivity and
569 1-specificity values for a range of predicted log WDI cut-off values. The area under
570 the ROC was found to be 0.70 ($p=0.05$).

571

572 Table 1. Characteristics of participants initiated on warfarin after cardiothoracic
573 surgery who consented to participate in the study (n = 41). One patient was an
574 emergency admission so a pre-operative weight was not documented (in this case the
575 first weight after surgery was used). Data are presented as the mean ± standard
576 deviation unless otherwise stated.
577

Characteristic	Descriptive Statistic
Age (years)	Median = 65 IQR = 56 - 71 (range = 28 - 85)
Gender n (%)	Male = 31 (76%) Female = 10 (24%)
Weight (kg) (n = 40)	Mean = 81 ± 19.4 (Range = 47 - 128)

578

579

580

581 Table 2. Indication for warfarin after cardiothoracic surgery for patients
582 participating in the study (n = 41).

583
584

Indication for Warfarin Therapy	n (%)
Mechanical Mitral Valve	10 (24.4)
Mechanical Aortic Valve	5 (12.2)
Tissue Mitral Valve	4 (9.8)
Mitral Valve Repair	11 (26.8)
Atrial Fibrillation	10 (24.4)
Left Ventricular Thrombus	1 (2.4)

585
586

587 Table 3. Linear regression model of predictors of log WDI with 95% confidence
 588 intervals reported in parentheses. Confidence intervals and standard errors (SE)
 589 based on 1000 bootstrap samples. Model 1 contains LVEF and Model 2 contains LVEF and
 590 length of cross-clamp time. $R^2=0.33$ for model 1 and $\Delta R^2=0.085$ for Model 2
 591 ($p=0.040$). SE=Standard error of the mean; CI=95% confidence interval
 592

Model	Coefficients (95% CI)	SE	P value
1. Constant	0.308 (- 0.071, 0.428)	0.092	0.069
LVEF	- 0.012 (- 0.15, - 0.008)	0.002	0.000352
2. Constant	0.026 (- 0.468, 0.425)	0.217	0.901
LVEF	- 0.011 (- 0.015, - 0.004)	0.003	0.000352
Cross-clamp time	0.002 (0.0001, 0.005)	0.001	0.040

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